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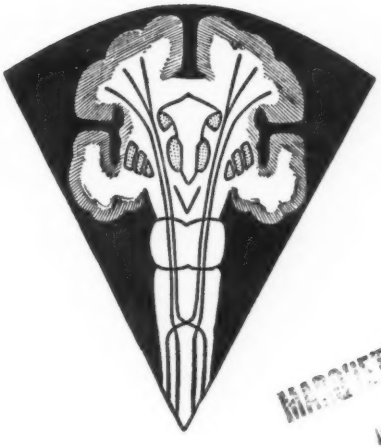

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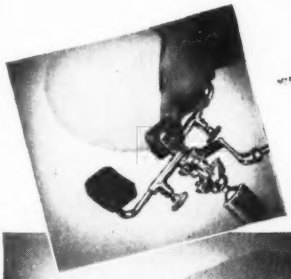

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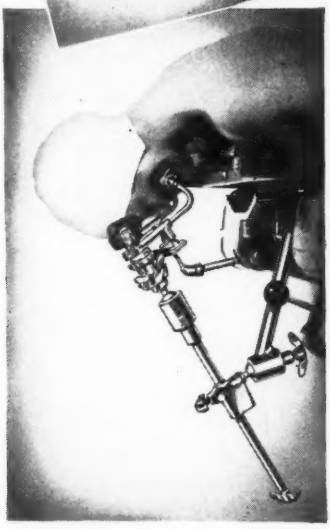

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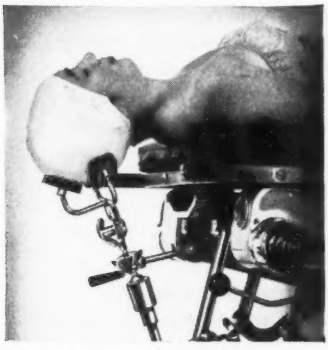

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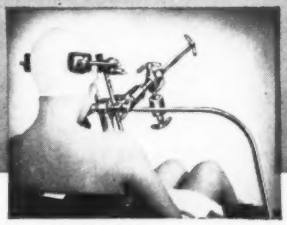

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History

The first investigation of a hemostat with an action comparable to Adrenosem Salicylate was made by Derouaux and Roskam[1] in 1937. They reported that an oxidation product of adrenalin, adrenochrome (which has no sympathomimetic properties), has prompt hemostatic activity.

It was further found that various combinations of adrenochrome, notably the oxime and semicarbazone, produced stable solutions. But, these were so slightly soluble that sufficient concentration could not be obtained for practical therapeutic use. By combining these adrenochrome compounds in a sodium salicylate complex a stable, soluble form can be obtained. This complex has been given the generic name, carbazochrome salicylate, and is supplied under the trade name Adrenosem Salicylate.

Roskam, in his study entitled "The Arrest of Bleeding,"[2] enumerates "the drugs whose efficaciousness as hemostatics have been proved by accurate methods in experimental animals and in healthy men as well. . . . One is the monosemicarbazone of adrenochrome [Adrenosem Salicylate]."

Chemistry

Adrenosem Salicylate is a synthetic chemical. The full chemical name is adrenochrome monosemicarbazone sodium salicylate complex.

Pharmacology

Although it is chemically related to epinephrine, Adrenosem Salicylate has no sympathomimetic effects. It does not alter blood components, nor does it affect blood pressure or cardiac rate.[2-7]

(* U.S. Patent 2,581,850)

Sherber, in an early study,[3] concludes that Adrenosem Salicylate* "is a potent antihemorrhagic factor in those conditions in which the integrity of the smaller vessels is interrupted, and is superior to any similar material that is now available."

He continues, "From our experience it appears that adrenochromazone complex is indicated in preventing vascular accidents incident to hypertension; in maintaining small vessel integrity; in the preoperative preparation where oozing from a vascular bed is anticipated, as in tonsillectomies, adenoidectomies and prostatectomies; and as an adjunct in the treatment of bleeding from such surgical procedures."

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Clinical investigators[2-7] are in agreement that Adrenosem Salicylate controls bleeding and oozing by decreasing capillary permeability and by promoting the retraction of severed capillary ends. It aids in maintaining normal capillary integrity by direct action on the intercellular "cement" in capillary walls. The interesting work of Fulton[8] confirms this. Adrenosem Salicylate, since it is not a vasoconstrictor, has no effect on large severed blood vessels and arterioles.

Adrenosem Salicylate is being used both prophylactically and therapeutically in thousands of hospitals, and in virtually every type of surgical procedure. It has also proved most useful in dental surgery.[7]

Owings reported on the use of Adrenosem Salicylate in controlling postoperative adenoid bleeding in 102 cases.[4] "We have used 2½ mg.

(½ ampule) intramuscularly, 15 minutes before anesthesia for children and 5 mg. (1 ampule) for adults." In only one patient did bleeding occur. Three others showed red blood from the nose and mouth. These patients "were then given 5 mg. intramuscularly, with prompt and complete control. We have also noticed that bleeding stopped more promptly on the operating table."

This is a 1% incidence of postoperative bleeding using Adrenosem Salicylate preoperatively, compared to an incidence of 10% postoperative bleeding in all cases taken from previous records, without Adrenosem Salicylate medication.

Peele reports on the use of Adrenosem Salicylate in treating 178 patients with 24 different conditions.[5] The drug was first used to control postoperative hemorrhage from the adenoid region. He adds: "The results were so dramatic that since that date [1953] Adrenosem Salicylate has been used postoperatively to reduce bleeding from all otolaryngologic and bronchoesophagolic procedures, to treat postoperative hemorrhage from the tonsil and adenoid regions, and to treat selected cases of epistaxis."

The effectiveness of Adrenosem Salicylate in controlling bleeding and oozing in 330 patients is reviewed by Bacala.[6] "Our experience of the effect of carbazochrome salicylate on 317 surgical indications and 13 obstetricogynecological conditions, has been therapeutically encouraging and successful for the control of capillary bleeding. Foremost among the cases studied were 223 tonsillectomies definitely benefited by this metabolic hemostat, making a diminution of the control incidence of posttonsillectomy bleeding of 19.8% down to 7%. It has also been found useful in gastro-intestinal bleeding, cataract extraction, epistaxis, incisional seepage, trans-urethral prostatectomy, menometrorrhagias, cervical ooze, antepartum and postpartum bleeding, threatened abortion, and prevention of capillary hemorrhages during hedulin or dicumerol therapy."

Side Effects

All investigators concur that, at recommended dosage levels, Adrenosem Salicylate is free from toxic effects. No cumulative effects attributable to the drug have been reported.

The only side reaction noted has been a transient stinging sensation in the area of injection when Adrenosem Salicylate is used intramuscularly. As one investigator comments: "The brief discomfort which attends the injection of Adrenosem into the gluteal region has not been a significant problem in children or adults as originally anticipated."[5]

Indications

Idiopathic purpura, retinal hemorrhage, familial telangiectasia, epistaxis, hemoptysis, hematuria.

Postoperative bleeding associated with:
tonsillectomy, adenoidectomy and
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For recommended dosage schedules, please send for detailed literature.

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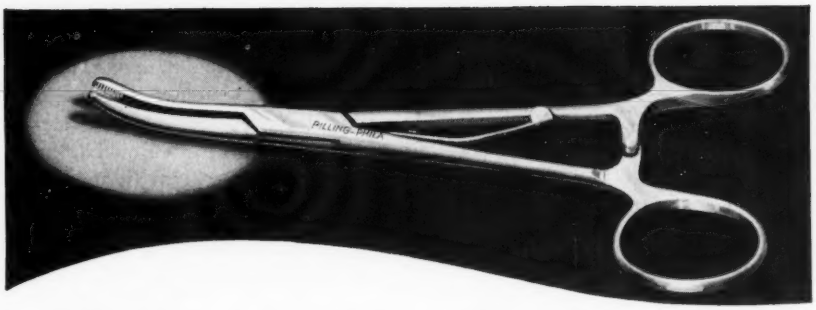

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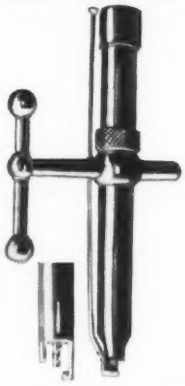

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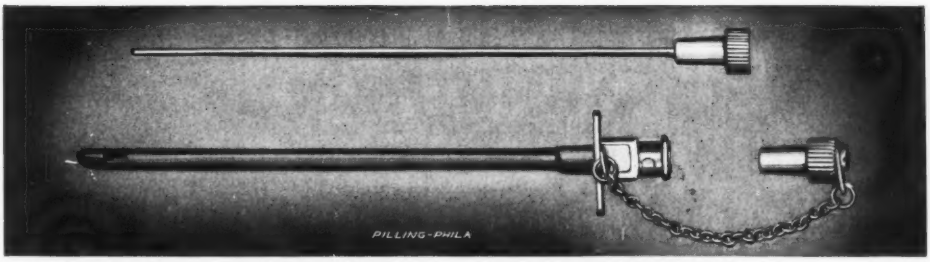

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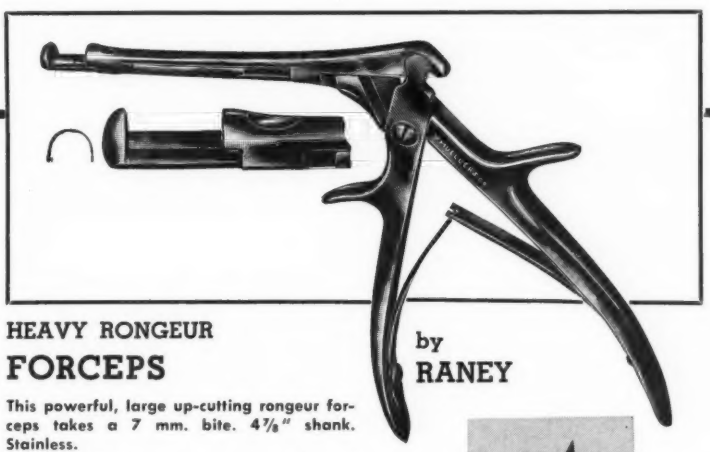

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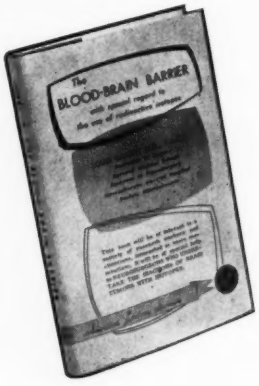

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with special regard to the use of radioactive isotopes

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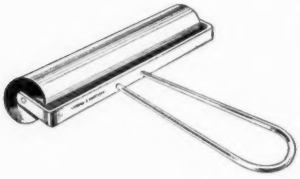

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FLUID AND ELECTROLYTE BALANCE FOLLOWING CRANIOTOMY*

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(Received for publication November 10, 1955)

METABOLIC balance studies, such as those performed by Moore and his co-workers,[21] have clarified the aberrations of fluid and electrolyte metabolism that occur during and following surgical procedures. The data thus obtained provided a rational basis for fluid and electrolyte administration during the operative and postoperative periods.

There are at least two important reasons for such investigations in patients with intracranial lesions. First, the electrolyte content of intravenous fluids, and possibly of body fluids, affects the cerebrospinal fluid pressure in animals[12,30,33] and in man.[3] Secondly, lesions in certain areas of the brain are associated with unusual abnormalities of electrolyte metabolism, e.g., "cerebral salt wasting"[24,32] and hypernatremia and hyperchloremia.[1,2,8,17,28]

In this paper, the results of metabolic balance studies in 2 patients following craniotomy and in 1 patient after ventriculography will be presented and studies in 5 other patients following craniotomy will be mentioned. In addition, 2 instances of marked hyponatremia which occurred after the removal of pituitary tumors will be described.

METHODS

The oral intake data were estimated from standard tables.[4] (Moore and Ball[21] stated that in their studies calculated intake data were close to the values obtained by analysis of the diet.) Sodium and potassium in urine and serum were measured on a Baird flame photometer with lithium as the internal standard.

The other determinations include 24-hour urinary excretion of nitrogen,[13] 17-ketosteroids[9] and free corticoids,[26] the concentration of eosinophils in peripheral blood,[27] and the serum chloride concentration[29] and carbon dioxide combining power.[23]

In Cases 1 and 2, in which balance data were fairly complete, the charting has been done according to the method of Moore and Ball.[21] The intake is charted upward from the base line, the output downward from the intake line. The difference is the net balance, which, if positive, is cross-lined above

* Supported in part by funds from Institutional Research Grant No. 43-F from the American Cancer Society.

the base line, if negative, is colored black below the base line. Thus, the intake, output, and net balance are visible at a glance. The other charts are explained in the legends.

CASE REPORTS

Case 1. A 12-year-old boy entered the University of California Hospital on Nov. 26, 1954. In September 1946 and again in March 1947, the patient had undergone

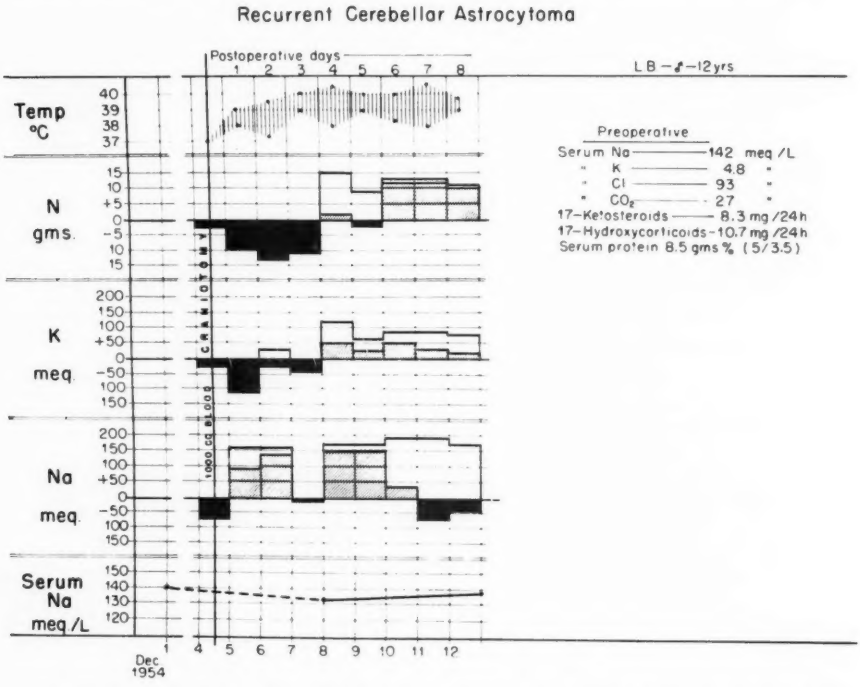
Recurrent Cerebellar Astrocytoma
Postoperative days
1 2 3 4 5 6 7 8
L B — ♂ — 12 yrs
Temp °C
40 39 38 37
N gms.
15 10 +5 0 −5 10 15
K meq.
200 150 100 +50 0 −50 100 150
Na meq.
200 150 100 +50 0 −50 100 150
Serum Na meq/L
150 140 130 120
Craniotomy
1000 cc. blood
Preoperative
Serum Na 142 meq/L
" K 4.8 "
" Cl 93 "
" CO_2 27 "
17-Ketosteroids 8.3 mg/24h
17-Hydroxycorticoids 10.7 mg/24h
Serum protein 8.5 gms% (5/3.5)
1 4 5 6 7 8 9 10 11 12
Dec 1954

FIG. 1. *Case 1.* From above downward: body temperature (°C.), nitrogen balance, potassium balance, sodium balance, and serum sodium concentration. The preoperative levels of serum electrolyte concentrations, urinary steroid excretion and serum protein are listed on the right side of the chart. The manner of depicting the balance data is described in the text under "Methods."

resection of a cystic cerebellar astrocytoma, followed by postoperative radiation therapy. He remained well from 1947 to October 1953, when occasional morning vomiting appeared. Subsequently, intermittent headaches, fatigability and ataxic gait developed.

On admission the significant clinical findings were underaction of the left lower face, a left extensor toe response (Babinski), and a tendency to fall to the left.

On Dec. 5, 1954 suboccipital craniectomy was performed, and a cerebellar astrocytoma extending into the cisterna magna was partially removed.

Except for hyperthermia, which persisted for several weeks, the patient's postoperative course was uneventful.

Metabolic Studies. The data of the balance study, charted in Fig. 1, demonstrated a metabolic response similar to that occurring after general surgical operations.[21] During the immediate postoperative period, the nitrogen and potassium balances were negative and the sodium balance was positive. In several days, these trends were reversed. Positive potassium balance began on the 4th postoperative

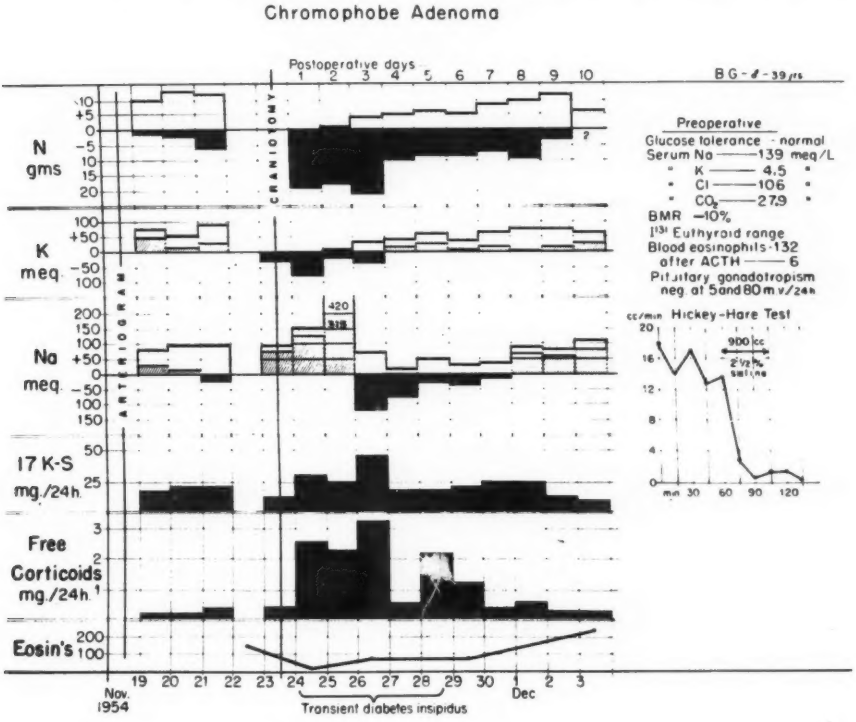

FIG. 2. *Case 2.* From above downward (left): nitrogen balance, potassium balance, sodium balance, 17-ketosteroid excretion, corticoid excretion and blood eosinophil concentration. On the right side of the chart are listed the preoperative data of glucose tolerance test, serum electrolyte concentration, basal metabolic rate, I^{131} uptake, blood eosinophil response to ACTH, pituitary gonadotropin excretion, and hypertonic saline test (Hickey-Hare). Postoperative serum sodium concentrations are listed in text description of case.

day, positive nitrogen balance on the 6th day, and negative sodium balance on the 7th day.

Oral feedings were begun on the 4th postoperative day, using a formula consisting of skimmed milk powder, banana flake and Meritene®. Accurate analysis of this formula, which was developed by Pickering,[25] had been previously performed.

During the immediate postoperative period, appreciable quantities of sodium were administered (see Fig. 1) because of the tendency of electrolyte-free intravenous fluids to increase the cerebrospinal fluid pressure,[3,12,30,33] and cause brain swelling.[31]

The other noteworthy point is the fall in serum sodium concentration to 133 mEq./l. on the 4th postoperative day, in spite of definite sodium retention. This "sodium paradox"[21] is the rule after trauma or major surgical procedures, and may be caused by a shift of sodium into the body cells[21,34] or a movement of cell water into extracellular fluid, thus decreasing sodium concentration.[34]

Case 2. A 39-year-old male was admitted to the Fort Miley Veterans Administration Hospital on Nov. 3, 1954. His symptoms included loss of libido and potentia during the preceding year, frontal headaches which had been present for 4 months, and failing vision of 2 months' duration.

Clinical examination disclosed bitemporal hemianopia; visual acuity was good. In roentgenograms of the skull, the sella turcica was enlarged. Tests to evaluate the level of endocrine function, listed in Fig. 2, revealed little evidence of hypopituitarism. The hypertonic saline test[6,16] was normal. Bilateral carotid angiograms were considered normal.

On November 23, without hormonal supplements, a right frontal craniotomy was performed under general anesthesia, and a cystic chromophobe adenoma of the pituitary was removed.

During the postoperative period, polyuria and polydipsia were present for several days, but no other complications occurred. Radiation therapy was subsequently administered. The visual fields improved promptly and were normal when the patient was last examined in February 1955.

Metabolic Studies. The balance data, steroid excretion and blood eosinophils are charted in Fig. 2. Again, the pattern is similar in general to that occurring after any major surgical procedure. The large sodium intake on the 2nd postoperative day was caused by an unexpectedly high oral intake in addition to 155 mEq. of sodium administered intravenously. Sodium diuresis appeared on the following day, but a second period of positive sodium balance supervened on the 8th postoperative day. Steroid excretion was elevated immediately after operation, then gradually fell to normal levels within a week. The serum sodium concentration (in mEq./l.) was 135 on the 1st postoperative day, 140 on the 3rd day, 135 on the 6th day, 133 on the 10th day, and 139 on the 14th day after operation.

Case 3. A 32-year-old male was admitted to the Fort Miley Veterans Administration Hospital on Jan. 27, 1955. The patient had noted a gradual onset of unsteadiness of gait and change in speech 7 years before. During the 6 weeks immediately prior to admission, these symptoms had progressed more rapidly. In addition, vague headaches and slight dysphagia had begun shortly before entry.

Examination on admission disclosed mild truncal ataxia, left dysdiadokokinesis and mild ataxia on left finger-to-nose test. Speech was somewhat thickened, and the left plantar toe response was equivocal. No nystagmus was present.

On February 3, biparietal trephination and ventriculography were done under local anesthesia with 1 per cent procaine. Premedication consisted of 100 mg. of a barbiturate and 0.6 mg. of atropine. Sixty-five cc. of ventricular fluid were replaced with air, and subsequent roentgenograms were interpreted as demonstrating moderate generalized ventricular enlargement. There was no evidence of an intracranial tumor.

The patient withstood the procedure well. His temperature was 100°F. on the afternoon of the day of operation but remained normal thereafter.

Metabolic Studies. During the first 7 days following ventriculography, the pa-

tient's only intake was a special formula, plus water as desired. Unfortunately, the exact figures of the daily amount of formula ingested were lost. However, except on the day of the procedure the patient consumed approximately two quarts of formula daily, containing about 60 mEq. of sodium and potassium and 12 gm. of nitrogen. Because the exact figures are not available, the electrolyte *output* only, not balance, has been charted in Fig. 3. These figures, together with the available intake data,

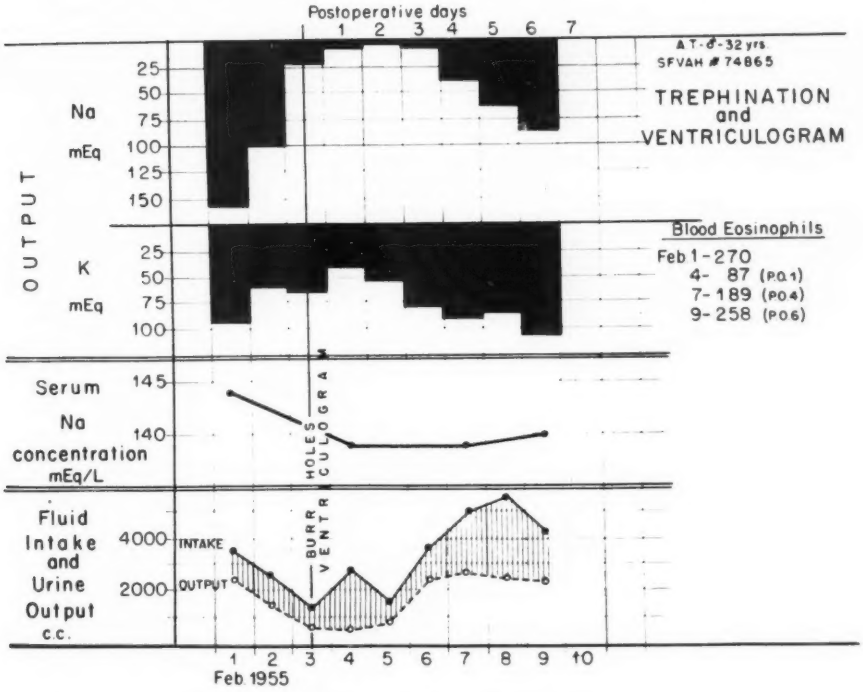

FIG. 3. *Case 3.* From above downward: Sodium *output*, potassium *output*, serum sodium concentration, and fluid balance. The concentrations of blood eosinophils are listed on the right. Output data should be compared with daily intake of 60 mEq. (approximate) each of sodium and potassium (see text).

indicate the development of two trends, i.e., relative oliguria and sodium retention. On the day of operation and the 1st and 2nd postoperative days, fluid intake was 5200 ml. and urinary output was 2100 ml. On the operative and first 3 postoperative days, the total urinary output of sodium was 40 mEq., while sodium intake was approximately 180 mEq. A moderate postoperative fall in blood eosinophils occurred. Negative nitrogen balance began on the 2nd postoperative day and a negative potassium balance on the 3rd. There was a slight fall in serum sodium concentration (143 mEq./l. to 138 mEq./l).

Five other patients who had craniotomies for intracranial tumors were studied from the standpoint of metabolic balance. The data are incomplete,

but from the information available, the metabolic response was qualitatively similar to that depicted in the foregoing cases.

Postoperative Hyponatremia. The next 2 patients were not studied by balance techniques, but are included because of the development of postoperative hyponatremia. The diagnosis in both instances was chromophobe adenoma of the pituitary.

Case 4. A 35-year-old female was admitted to the University of California Hospital on Oct. 20, 1954. Symptoms included amenorrhea (4 years), headaches (3 months), and impaired vision and diplopia (1 month). Bitemporal hemianopia was present, and loss of central vision had occurred on the right. Basal metabolic rate was plus 3 per cent, and protein-bound iodine was 4.9 μg./100 cc. (normal 4 to 8). The 24-hour urinary excretion of 17-ketosteroids, which was initially 2.5 mg., rose to 5.4 mg. following the administration of corticotrophin.

On Oct. 25, 1954, a right frontal craniotomy was performed under general anesthesia, and a large chromophobe adenoma of the pituitary was partially removed.

The patient was alert on the 1st postoperative day but became stuporous on the 2nd day. The craniotomy was re-explored, but no hematoma was found. On the 3rd day, a tracheotomy was done. The patient gradually improved and oral feedings were begun on the 6th postoperative day. Her temperature, which had risen to 40°C. (104°F.) on the 2nd postoperative day, was 37.5°C. (99.5°F.) on the 4th day. After removal of the tracheotomy tube, the patient was discharged on Nov. 10, 1954.

Metabolic Studies. Available data are charted in Fig. 4. It is evident that marked hyponatremia (116 mEq./l.) occurred on the 2nd postoperative day. Some degree of depression of adrenal function was probably present. However, on the 5th postoperative day, when the serum sodium concentration had risen to 141 mEq./l., the urinary sodium concentration was only 4 mEq./l., suggesting adequate renal conservation of sodium.

Dilution of the extracellular sodium, in addition to the usual postoperative fall in serum sodium concentration, probably contributed to the hyponatremia. On the day of operation and the 1st postoperative day, the patient received 4000 ml. of water, intravenously, but only 39 mEq. of sodium. The exact urinary output on the 1st postoperative day is not known, but it was small. For the 2 days, the urinary output was probably not more than 800 ml. Allowing for an insensible water loss of 600 to 850 ml. per day,[22] the patient retained between 1.5 and 2 liters of water in this 2-day period, with less than 40 mEq. of sodium. As soon as the sodium intake was increased and the urinary volume increased, the serum sodium concentration rose and the patient improved rapidly.

Water intoxication has been observed in general surgical patients, sometimes in instances in which fluid intake has not seemed excessive.[35] Dudley *et al.*[10] believe that the mechanism of water intoxication is probably more complicated than simply hypotonicity of the extracellular fluid. Hypophysial and adrenal insufficiency increase susceptibility to water intoxication.[14]

Case 5. A 48-year-old female had had a right frontal craniotomy and removal of a chromophobe adenoma of the pituitary in 1947. Four years later, diabetes mellitus was discovered and the patient was placed on 10 units of protamine zinc insulin daily. Three years after this, vision again began to fail.

When the patient was readmitted to the University of California Hospital, on

Jan. 23, 1955, the visual field of the right eye was reduced to a small island in the inferior nasal quadrant. There was loss of most of the temporal field of the left eye, but left visual acuity was good.

At re-operation on Jan. 31, 1955, a recurrent pituitary chromophobe adenoma was removed.

During the next 7 days, 3 to 4 plus glycosuria and slight acetonuria were present, despite administration of regular insulin. Acetonuria then ceased, and the urine was maintained sugar-free.

The patient's conscious state was satisfactory for 3 days after operation, following which she became restless and drowsy. The trend reached its maximum on the

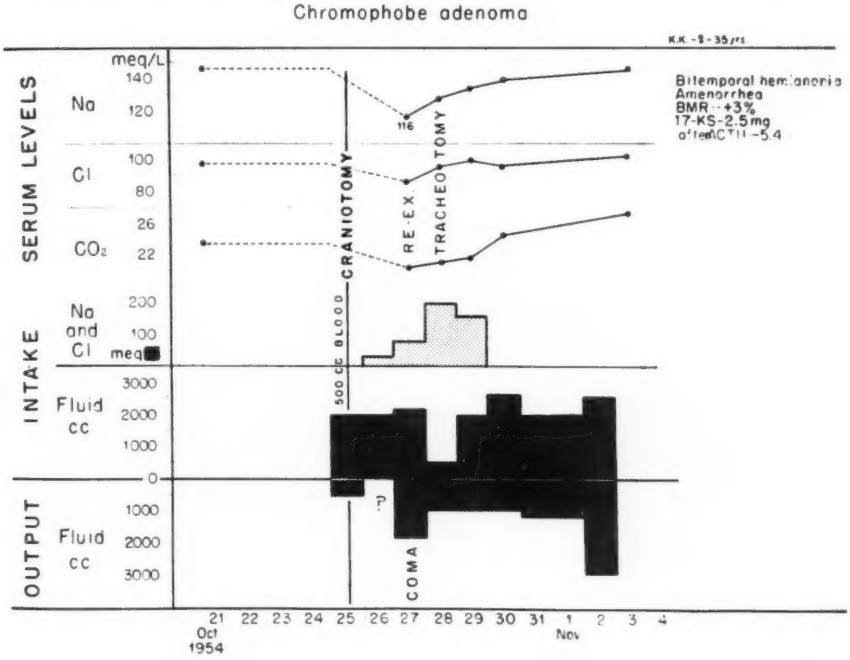

FIG. 4. *Case 4.* From above downward: serum sodium concentration, serum chloride, serum CO_2, sodium and chloride intake, fluid intake, and urinary output. Preoperative basal metabolic rate and response of 17-ketosteroid excretion to ACTH administration are listed on right side of chart.

5th and 6th postoperative days, when a deep stupor developed and the patient's temperature rose to 39.4°C. (102.9°F.). Spinal fluid pressure at that time was 560 mm. of water. During the 6th and 7th postoperative days, 500 ml. of 3 per cent saline were administered, and the patient began to rouse. On the 8th day, she was able to eat and 4 days later she was discharged.

One month after discharge, the left visual field had improved, although the field of the right eye was unchanged. Twenty units of insulin per day were necessary to prevent glycosuria.

Metabolic Studies. The data in this case are shown in Fig. 5. Unfortunately, the

daily electrolyte intake and output were not determined except for the intravenous fluids listed at the bottom of Fig. 5. The cause of hyponatremia was more complex than in Case 4. Renal loss of sodium was probably appreciable, because of glycosuria and acetonuria.

Postoperative oliguria and positive water balance also occurred in this patient. These factors were particularly marked on the 4th postoperative day, when the intake was 3000 ml. and the urinary output was only 650 ml., resulting in a positive

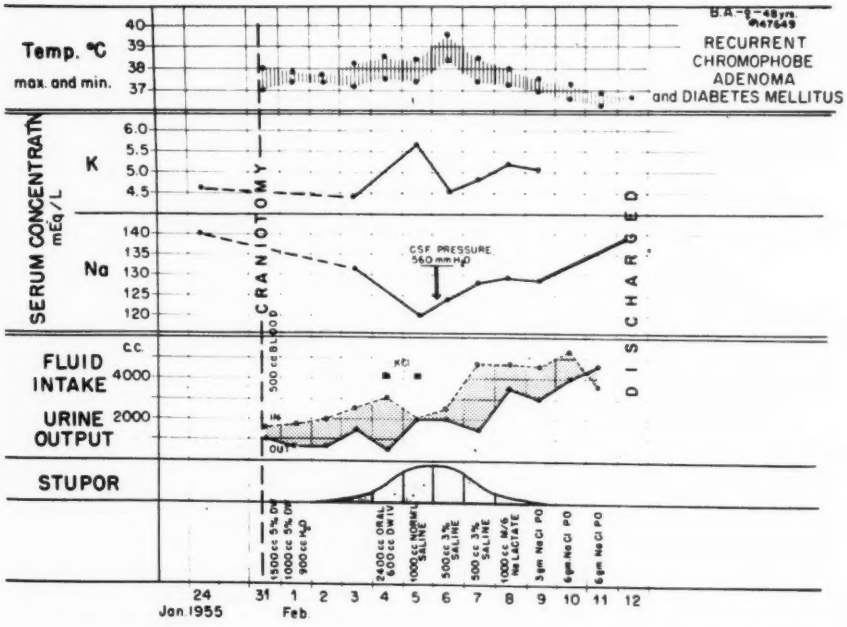

FIG. 5. *Case 5.* From above downward: body temperature range (°C.), serum potassium concentration, serum sodium concentration, fluid intake, urine output, estimate of degree of stupor and partial data of electrolyte intake. KCl indicates additional potassium chloride administered intravenously on February 4 and 5.

water balance of between 1500 and 1750 ml. (allowing for insensible loss). On the following day, when the patient was deeply stuporous, the serum sodium concentration was 120 mEq./l., and the serum potassium 5.7 mEq./l. The next morning, spinal fluid pressure was found to be markedly elevated. The administration of hypertonic saline resulted in fairly prompt response, and the patient was alert enough to eat on the 8th postoperative day. It should be noted that the serum sodium concentration barely rose on the 8th and 9th postoperative days (in spite of the high sodium intake), probably because of the strongly positive water balance on the previous day (intake 4540 ml., output 1550 ml.). The final serum sodium concentration was 139 mEq./l. on the day of discharge.

DISCUSSION

These studies delineate a metabolic response to craniotomy which is quite similar to that noted after other surgical procedures. The negative potassium and nitrogen balances and the positive sodium balance which occur initially are followed in several days by a reversal of these trends. In apparent direct contradiction to the net balance, the serum sodium concentration tends to fall initially, and the serum potassium to rise. Case 3 is of particular interest in that a procedure under local anesthesia involving minimal surgical trauma induced a fairly strong response, especially in regard to sodium retention and oliguria. Perhaps irritation of the ventricular walls by air stimulated the hypothalamus, which in turn activated the anterior and posterior lobes of the pituitary.[15]

Cases 4 and 5 illustrate the development of hyponatremia following craniotomy. Because of the impaired state of consciousness, both patients were suspected of having intracranial hematomas, and in one, re-exploration was carried out. The rapid improvement following administration of hypertonic saline was striking, and no hormonal supplements were necessary.

Postoperative oliguria appears to have played an important role in the development of the hyponatremia. The oliguria, which has been noted after other surgical procedures,[19,20] tends to vary with the severity of the operation and is not affected by replacement of operative blood loss or a large intake of fluid.[7] It does not depend on sodium retention, but is presumed to be caused by release of antidiuretic hormone.[10,18] Case 3, in which there was only minimal trauma to tissues and no general anesthetic would tend to support the theory that oliguria is of posterior pituitary origin.

Data presented in two recent studies of patients who had mitral valvulotomy are pertinent to this problem. Wilson *et al.*[34] allowed 60 patients unlimited fluid intake in the immediate postoperative period, while 30 patients were restricted to 1500 ml. per day. The two groups allowed unrestricted fluids drank 3210 ml. and 3460 ml. more in a 3-day period, but excreted only 850 ml. and 810 ml. more urine, respectively, than the group whose fluids were restricted. Associated with this fluid retention, there was a greater fall in serum sodium concentration than in the fluid-restricted group. In explaining the postoperative fall in serum sodium concentration, however, the authors stated that " 'external dilution' is not the only significant factor, if it is assumed that the retained water is evenly distributed over the body."[34] Some workers have suggested that this retained water remains largely in the extracellular space.[18,20]

Bruce *et al.*[5] divided their patients into three groups. Twelve patients (Group I) were allowed unrestricted fluids postoperatively but no saline. Eighteen patients (Group II) were given unrestricted fluids plus some saline (average 61 mEq. of sodium per day). Ten patients (Group III) were allowed less than 1 liter of water per day and no saline. The incidence of hyponatremia (serum sodium below 127 mEq./l., in this instance) was 33 per cent

in Group I, 39 per cent in Group II, and 10 per cent in Group III. The average for each group showed a greater fall in serum sodium in Groups I and II than in Group III. In 2 patients in Group I (unrestricted fluids) there developed marked hyponatremia, associated with stupor and delirium. They improved promptly when saline was administered.

These two studies suggest that retention of water (without sodium) plays a role in the usual postoperative fall in serum sodium concentration, by diluting the sodium present. Dudley *et al.*[10] found that retention of water in the postoperative period resulted in a decrease of serum sodium concentration greater than that calculated from simple dilution (assuming the retained water is equilibrated with total body water). Other suggested mechanisms include intracellular shift of sodium[21,34] or "internal dilution" by cell water.[34]

In determining the type of intravenous fluids to be given during and after craniotomy, the metabolic response to the operative procedure must be considered. It has been suggested that intravenous solutions of 2.5 per cent glucose in 0.42 per cent sodium chloride[3] or sodium lactate[33] be used during and following craniotomy to avoid the brain swelling which may be caused by electrolyte-free fluids. In patients who have had craniotomy on the Neurosurgical Service at the University of California Hospital, 0.45 per cent saline has been used in selected cases for several years without any apparent adverse effects. However, the postoperative sodium retention may be dangerous in patients with cardiac disease. Two of the patients reported by Bruce *et al.*[5] were allowed unlimited fluids and some saline (about 60 mEq. per day) following mitral valvulotomy. After intravenous administration of sodium lactate, both patients died of acute pulmonary edema.

Restriction of fluid intake during the operative and postoperative period may minimize postoperative hyponatremia with its attendant risk of cerebral edema. This was suggested in the treatment of head trauma some years ago by Fay.[11] However, the severe restriction of fluid intake (600 cc. per day) which he advocated may result in dehydration.

Dehydration is not advocated, but rather careful avoidance of overhydration. Wilson *et al.*[34] demonstrated that increasing the postoperative fluid intake does not result in a commensurate increase in urine output, but in fluid retention. Their restricted fluid intake was 1500 ml. per day, while Bruce *et al.*[5] allowed less than 1 liter per day. Studies in patients without cardiac disease supported these conclusions.[7,10,18,35] However, severe restriction in fluid intake may be associated with some increased danger of venous thrombosis.

No single arbitrary figure for fluid intake can be proposed because of variables, such as climate, body weight and body temperature, which affect fluid loss. If sodium-containing fluids are administered, the amount is less critical, except insofar as total body water and cardiac status are concerned. If electrolyte-free fluids are used, the volume must be calculated according to output of urine, presumed insensible loss, and extrarenal loss. Oliguria may occur and persist for several days after craniotomy. A daily urinary

volume of 500 to 700 ml. is thought to be adequate during the first 2 days following a major surgical procedure.[10] An attempt to maintain an arbitrary higher urinary volume during this time by forcing fluids may result in marked fluid retention.

The simplest indicator of fluid retention is the daily weight of the patient. A patient should lose weight after an operation.[10,21] Postoperative increase in weight is "an outstanding abnormality of surgical metabolism,"[34] and generally indicates retention of fluid.

SUMMARY

Studies of the metabolic response to craniotomy are reported. The data obtained indicate that the metabolic alterations are similar to those noted after other surgical procedures and include sodium retention, potassium loss, nitrogen loss, and frequently oliguria. These trends are reversed in several days.

Two patients in whom hyponatremia developed following craniotomy for pituitary tumors are described. Fluid retention without sodium administration appeared to be partially responsible for the hyponatremia. The patients were comatose when the serum sodium concentration was low and regained consciousness shortly after the administration of hypertonic saline.

The type and amount of intravenous fluid to be administered during and following craniotomy are discussed in the light of these studies.

The laboratory studies in Cases 2 and 3 were done under the direction of Dr. T. V. Feichtmeir, Chief of the Clinical Laboratory at Fort Miley Veterans Administration Hospital. In the remaining cases, the studies were done in the Central Laboratory of the University of California Hospital (Dr. W. L. Bostick, Director). Miss Kay Hyde drew the charts. The author is also indebted to Dr. E. B. Boldrey and Dr. I. S. Edelman for valuable advice and criticism, and to Mrs. M. Beaghler for editorial assistance.

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DEEP HYPOTHERMIA IN INTRACRANIAL SURGERY*

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IN ORDER to evaluate the effect of low body temperature in intracranial surgery, we have carried out 18 major brain operations under medium deep and deep† hypothermia. The series consisted of 14 cases of brain tumour and 4 cases of vascular malformation. This is a preliminary report on our experiences from a neurosurgical point of view. Problems bearing on the general effects of hypothermia lie beyond the scope of the present communication and will not be discussed in detail.

General hypothermia was introduced into practical medicine in 1939 by Smith and Fay,[23,24] who used the method in the treatment of cancer. Fay[11] was also the first to employ hypothermia as an adjuvant in neurosurgery. With a "cooling blanket" he lowered the body temperature of patients with head injuries and hyperthermia to about 33.0°C. (91.4°F.).

In 1951 a different method for lowering the body temperature was introduced by Laborit and Huguenard[14] under the name of *hibernation artificielle*. This method, in which a superficial hypothermia is induced mainly by means of different drugs ("lytic cocktail"), has been used in intracranial surgery by Lazorthes *et al.*[15] and by Woringer *et al.*[29]

In 1950 Bigelow *et al.*[4] and in 1951 Boerema *et al.*[7] showed that at a body temperature of 20°C. (68°F.) dogs can survive total occlusion of the circulation during any time up to 15 minutes without sequelae from cerebral hypoxia being demonstrable on restoration of normal body temperature. Bigelow *et al.*[5] also found that oxygen consumption decreased almost linearly with lowering of the temperature, provided that shivering was prevented by the administration of appropriate anesthetics and arterial oxygen saturation was maintained at a high level, and that under these conditions a tissue oxygen deficit did not develop during the cooling period. It is on the basis of these fundamental experiments that hypothermia has been utilized for the last 3 years in cardiac surgery to permit intracardiac operations under visual control. Communications on these investigations have been published by Lewis *et al.*,[16] Swan *et al.*,[26] Bailey *et al.*[2] and others.

Hemorrhage, increased intracranial pressure, acute brain swelling and local cerebral hypoxia still render many intracranial procedures hazardous.

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† In this paper "deep" hypothermia is to be understood as 27.0°C. (80.6°F.) and below, "medium deep" as 27.1°–32.0°C. (80.8°–89.6°F.) and "superficial" as above 32.0°C. (89.6°F.).

These complications are responsible for most of the postoperative neurological sequelae and deaths, and are the main cause of most of the difficulties encountered in brain surgery.

Despite the advances made in methods of hemostasis, the prevention of *hemorrhage* during or after an operation is still an important problem for the neurosurgeon. The introduction of induced hypotension by ganglionic blocking agents in 1948 marked a great advance, especially in the surgery of vascular malformations. It has long been known that the blood pressure decreases with lowering of the body temperature,[28] but the underlying mechanism appears to differ widely from that of hypotension induced by ganglionic blocking agents.

Studies on cerebral hemodynamics in man[9,18,25] indicate that the fall in blood pressure in the cerebral arteries accompanying ganglionic block is compensated by a corresponding decrease in the peripheral resistance caused by vasodilatation, with the result that the cerebral blood flow is still sufficient for satisfactory oxygenation of the brain. Stone *et al.*[25] found complete compensation at blood-pressure levels as low as 31 to 60 mm. Hg in 4 cases, but they pointed out that these results do not permit generalization, since many different factors, such as general anesthesia or arteriosclerosis of the cerebral arteries, might cause compensation to be incomplete. It seems reasonable to suggest that increased intracranial pressure may act similarly by deranging cerebrovascular dynamics. In hypothermia, on the other hand, the consumption of oxygen decreases simultaneously with the fall in blood pressure: oxygenation of the tissues is still satisfactory, despite low arterial pressure, peripheral vasoconstriction and diminished blood flow. In experiments on dogs Bigelow *et al.*[5] found this to hold down to a temperature of 19.0°C. (66.2°F.) for up to 4 hours (blood pressure between 20 and 40 mm. Hg).

Clinical investigations of the side effects of induced hypotension show that this method involves certain risks of damage to the brain and other organs by hypoxia. By means of questionnaires to British anesthetists, Hampton and Little[12] collected information about 21,000 cases in which hypotension had been induced by ganglionic blocking agents. There were 42 deaths (0.2 per cent), probably ascribable to the hypotension. Statistical evaluation suggested that 80 mm. Hg is a critical level, above which complications are infrequent. The incidence of cerebral hypoxia cannot be estimated from these series. Berg[3] and Nilsson,[19] using flicker fusion after administration of Evipan as a test of cerebral function, found values supposed to indicate diffuse cerebral injury in 12 of 29 patients operated upon extracranially under induced hypotension with blood pressures between 60 and 80 mm. Hg. As to deep hypothermia, no comparable investigations are available, but, as far as we know, no experimental or clinical data available show that hypothermia involves a risk of cerebral hypoxia (provided that ventilation is sufficient and shivering is prevented). Smith[22] reviewed a number of patients with cancer treated with hypothermia. He found no signs of mental dis-

turbances, and at 50 autopsies he could not detect any evidence of injury from cerebral hypoxia. Callaghan *et al.*[8] induced hypothermia (20°C., 68°F.) in monkeys. After rewarming they could not find any signs of mental disorder or electroencephalographic abnormalities.

The above-mentioned investigations suggest the following conclusion: In hypotension induced by ganglioplegic agents hemodynamic mechanisms try to maintain cerebral blood flow at a normal level by means of vasodilatation. Under certain circumstances, however, these mechanisms fail and thereby create the risk of cerebral hypoxia, this risk being increased below a critical level of 80 mm. Hg. In hypothermia the low blood pressure is accompanied by a decrease in cerebral blood flow. Nevertheless the risks of cere-

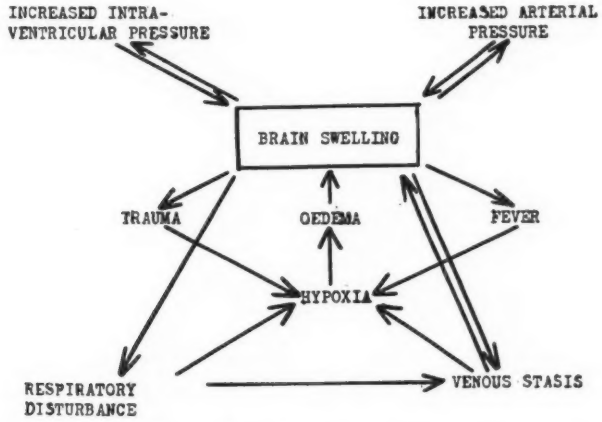

FIG. 1. Diagram illustrating the interplay of different factors suggested as possibly producing increased intracranial pressure and brain swelling.

bral hypoxia seem to be less than at normal body temperature, even if the blood-pressure level is far below 80 mm. Hg.

Increased intracranial pressure and swelling of the brain are complex phenomena correlated with many factors, several of which are themselves correlated. This explains the tendency to the development of a frequently fatal vicious cycle. We have tried to depict the interplay of these factors diagrammatically in Fig. 1, which is based on well known clinical and experimental observations.

The interrelationships apparent from the diagram suggest that hypothermia might be able to diminish or counteract swelling of the brain by diminishing the risk of general hypoxia and decreasing the cerebral blood pressure and blood flow. The above-mentioned studies on cerebral blood flow in hypotension induced by ganglioplegic agents indicate that these agents do not produce any decrease in the volume of the brain. This is in line with our clinical experience that induced hypotension has only a slight

effect, if any, on the persistent increase in intracranial pressure in cases of brain tumours. Obrador *et al.*[20] made similar observations in an experimental and clinical investigation. In contrast therewith they found a clear effect of ganglioplegic agents on sudden increase of intracranial pressure and brain volume produced in dogs by lesions of the floor of the fourth ventricle as well as on the acute swelling of the brain that sometimes occurs in humans during intracranial operations. In the present investigation special interest was focused on the effect of hypothermia on increased intracranial pressure and acute swelling of the brain.

Local cerebral hypoxia with consequent functional disorders must always be taken into consideration when manipulation of large arteries or veins is necessary during an intracranial procedure. Functional disturbances after direct traumatisation of the brain tissue during an operation can probably also be at least partly ascribed to disturbance of the circulation with consequent local hypoxia. It is known from Bigelow *et al.*[4] that the risk of general hypoxia and its sequelae after temporary occlusion of the blood supply to the brain decreases with lowering of the body temperature. It does not sound unreasonable to suppose that this might also hold for lesions from local hypoxia, especially if the lesions are caused by reversible circulatory disturbances such as ligation of parasagittal veins, spastic arterial constriction, temporary clamping of a cerebral artery or pressure on the brain. Judging by the experiments of Ralston *et al.*[21] and Thompson and Smith[27] on dogs, hypotension produced by loss of blood or ganglionic blocking agents enhances the cerebral injury following ligation of the middle cerebral artery. These investigations suggest that, as far as local hypoxia is concerned, deep hypothermia implies better surgical conditions than those prevalent in normothermic patients with or without hypotension induced by means of ganglionic blocking.

When planning the present investigation there were thus ample experimental and clinical data available suggesting that deep hypothermia might imply certain advantages in intracranial surgery, especially with regard to hemorrhage, increased intracranial pressure, brain swelling and lesions from local hypoxia. Our decision to try deep hypothermia in brain operations was preceded by experimental work with special reference to the effect of hypothermia on different kinds of brain lesions (unpublished). It was the experience gained thereby that guided our choice of technique for the induction of hypothermia in the clinical trial.

The risks of deep hypothermia were known beforehand from experimental studies on animals and from clinical reports of surgery on the open heart. In the clinical series ventricular fibrillation was responsible for most of the postoperative deaths. In the 3 largest series,[2,16,26] including 34 cases in all, ventricular fibrillation occurred in 13 cases with 6 fatalities. In only 3 cases did fibrillation start before the heart had been exposed, apparently at body temperatures between 27.0°C., and 30.0°C. (80.6°F.–86.0°F.). It sounds reasonable to suppose that the risk of ventricular fibrillation is less in pa-

tients without severe organic heart disease and operated upon without manipulation of the exposed heart. On the other hand, in cases of emergency, countermeasures can be taken with less loss of time if the thorax is open. It was mainly because of the risk of cardiac complications that the first 6 operations in the present series were carried out on patients with gliomata or metastases in the brain. No patients with serious organic heart disease were accepted for hypothermia. Apart from this, the patients were not selected according to any standardized criteria.

METHOD

Hypothermia was induced and body temperature was restored by means of circulating air in an apparatus described by Lundberg and Nielsen.[17]* The design and mode of action of the apparatus are apparent from Fig. 2.

The anesthetic procedure was as follows. The usual premedication was given: to patients with symptoms or signs of increased intracranial pressure phenobarbital

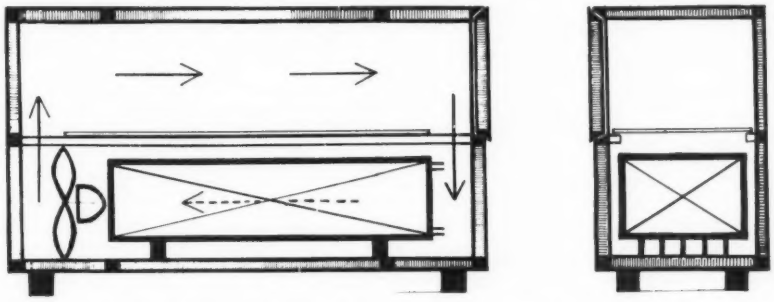

FIG. 2. Schematic design of the apparatus for cooling and rewarming.

and atropine; to the remainder phenobarbital, morphine and scopolamine. Anesthesia was induced with a basic dose of Evipan (200–400 mg.), after which the patient was intubated with a cuff-tube, relaxation being secured by succinylcholine-chloride. Anesthesia was maintained by inhalation of nitrous oxide and ether. In order to get the shivering under control from the very beginning of the cooling procedure, we aimed at securing moderately deep anesthesia (third stage, plane 2) before it was started.

As soon as the anesthesia was considered deep enough, the patient was placed in the cold box and connected to the anesthesia machine and the equipment for recording blood pressure and body temperature as well as to the electrocardiograph. In order to insure adequate ventilation throughout the procedure of hypothermia, the respiration of the patient was taken over by a respirator† during the period of active cooling, i.e., before the body temperature reached 30°C. (86°F.). In the beginning the patient's hands, feet and external genital organs were protected, but later this practice was found unnecessary. The temperature in the box was maintained at a fairly constant level between −5°C. and −10°C. (23°–14°F.). In all cases except 3, active cooling was interrupted at a rectal temperature of about

* Manufactured by Atlas, Copenhagen.

† "Aga Vivrator," Aga, Stockholm.

30°C. (86°F.), which was reached after an average of 2 hours, 20 minutes (range: 3 hours, 20 minutes–1 hour, 25 minutes).

As soon as the patient was removed from the box, he was laid on the operating table, and the operation was started after catheterization of the radial artery and a subcutaneous vein. The rectal temperature continued to fall after active cooling had been stopped: at the beginning of the operation it varied between 28.0° and 29.0°C. (82.4–84.2°F.); 1–1½ hours after the end of active cooling the fall in temperature ceased at between 24.8°C. and 27.0°C. (76.6°–80.6°F.). The rectal temperature persisted at this low level until rewarming was started, in one case as long as 8 hours (see Fig. 3).

Continuous infusion of 5 per cent glucose by intravenous drip and one or two infusions of 500 ml. citrated blood were routine measures. In 2 cases Arfonad* in a 0.1 per cent solution was administered by intravenous drip.

The rewarming procedure was varied. After the operation the patients were usually placed in the box in which the temperature was maintained at 35°–40°C. (95°–104°F.) with the fan running. Rewarming to 34.0°C. (93.2°F.) usually required 3–4 hours. During this period shivering could usually be controlled with nitrous oxide only. In some cases the patients also received chlorpromazine in one or more doses of 50 mg. After the rectal temperature had increased to about 34.0°C. (93.2°F.) the patient was put to bed and transported to the ward. In some cases rewarming was intentionally retarded: on conclusion of the operation the patient was immediately placed in bed and removed to a room with a thermostatically controlled temperature of 30°C.–35°C. (86°–95°F.). In one instance (Case 7) recovery of body temperature to 34.0°C. (93.2°F.) required 11 hours (see Fig. 3). The respirator was disconnected during the rewarming period at varying levels of temperature from 26.0°C.–34.0°C. (78.8°–93.2°F.).

The rectal temperature was measured with a thermocouple and a mirror galvanometer,† and the blood pressure by sphygmomanometer and palpation of the radial pulse. (All blood-pressure values in this paper are therefore only approximate and are given to the nearest degree.) The electrocardiograms were recorded by a direct writing apparatus‡ and could also be followed continuously on the screen of a cathode-ray oscillograph.§ This equipment also permitted continuous recording of the muscle activity in association with shivering.

RESULTS

Mortality. Two deaths (Cases 10 and 11) occurred in this series (operative mortality 11 per cent). In Case 10 postmortem examination revealed diffuse purulent meningo-encephalitis, the origin of which could not be explained. In Case 11 the cause of death was increased intracranial pressure from multiple metastatic tumours in the brain and possibly accentuated by the operative trauma. In neither of the 2 fatal cases did the postoperative course or the postmortem examination reveal anything suggesting that the hypothermia per se had played a contributory rôle as a cause of death. This possibility, however, cannot be excluded with certainty.

* Manufactured by Hoffmann-La Roche, Inc., Basel, Switzerland.
† "Electric Universal Thermometer" type TE 3, Elektrolaboratoriet, Copenhagen.
‡ "Mingograf," type 23, Elema, Stockholm.
§ "Cardioscope," Elema, Stockholm.

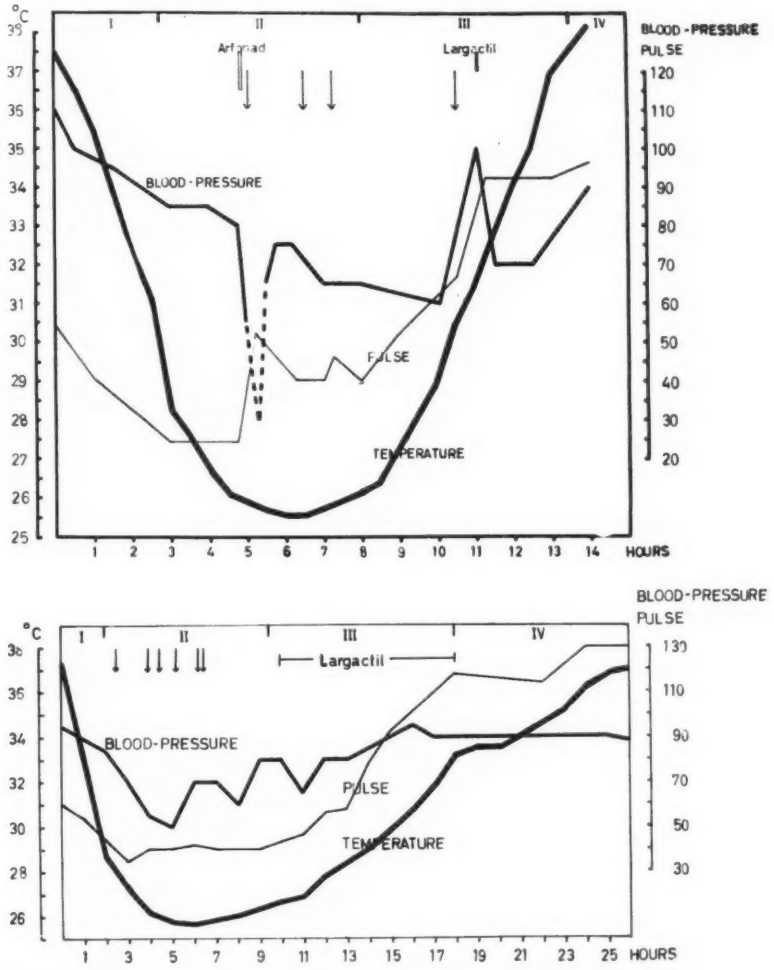

FIG. 3. Diagrams illustrating the fluctuations of rectal temperature, blood pressure and pulse during hypothermia in two different cases. (I) Cooling in the box. (II) Operation. (III) Rewarming. (IV) Patient back in the ward. ↓ indicates transfusion.

(*Above*) Case 10. Male. Aged 58 years. Intracranial ligature of arterial aneurysm from anterior communicating artery.

(*Below*) Case 7. Female. Aged 43 years. Partial removal of meningioma from clivus and left petrous bone.

Extracerebral Complications. Ventricular fibrillation did not occur in any of the patients.* Electrocardiographic abnormalities (arrhythmia, extrasystole, deformation of the auricular and ventricular complexes) were re-

* Since this series was presented we have had one case of ventricular fibrillation with fatal outcome.

TABLE 1

Case No.	Age Sex	Diagnosis	Operation	Cooling Time	Rectal Temp. at End of Cooling °C. (°F.)	Lowest Rectal Temp. °C. (°F.)	Lowest Blood Pressure (mm. Hg)	Operating Time	Rewarming Time (to 34° C.)	Postoperative Complications
1.	48 M	Metastatic carcinoma, lt. occipital. Bronchial carcinoma	Extirpation	3 hrs.	29.6 (85.3)	29.2 (84.6)	90	3 hrs.	5 hrs.	
2.	31 F	Astrocytoma, rt. frontal	Resection of frontal lobe	2 hrs.	30.0 (86.0)	28.5 (83.3)	90	2 hrs., 50 min.	2 hrs.	
3.	62 M	Glioblastoma, rt. parietal	Partial extirpation	2 hrs., 25 min.	29.4 (84.9)	25.1 (77.2)	50	3 hrs.	7 hrs.	
4.	57 M	Gliblastoma, rt. parieto-occipital	Extirpation	3 hrs., 20 min.	29.9 (85.8)	24.8 (76.7)	<50	3 hrs., 45 min.	4 hrs., 40 min.	
5.	47 F	Glioblastoma, lt. parietal	Extirpation	2 hrs., 15 min.	31.3 (88.4)	27.0 (80.6)	75	3 hrs.	4 hrs., 15 min.	
6.	61 F	Glioblastoma, rt. frontal	Resection of frontal lobe	1 hr., 45 min.	31.2 (88.2)	27.2 (81.0)	65	2 hrs., 40 min.	3 hrs., 15 min.	
7.	43 F	Meningioma, clivus and lt. pyramid	Partial extirpation	2 hrs.	29.9 (85.8)	25.7 (78.3)	50	7 hrs., 30 min.	10 hrs.	
8.	47 M	Aneurysm, ant. communicating artery	Intracranial ligature	3 hrs., 15 min.	30.7 (87.3)	26.6 (79.9)	40	4 hrs., 20 min.	3 hrs., 30 min.	
9.	22 F	Arteriovenous aneurysm, rt. parietal	Extirpation	2 hrs., 15 min.	30.0 (86.0)	24.8 (76.7)	45	4 hrs.	3 hrs., 50 min.	
10.	58 M	Aneurysm, ant. communicating artery	Intracranial ligature	3 hrs.	30.0 (86.0)	25.5 (78.0)	45	4 hrs., 10 min.	4 hrs.	Diffuse purulent hemorrhagic encephalo-meningitis. Died 7th postop. day
11.	51 M	Multiple cancer metastases to brain. Bronchial carcinoma	Extirpation of temporal metastasis	1 hr., 45 min.	30.3 (86.5)	24.9 (76.8)	50	3 hrs., 15 min.	3 hrs., 30 min.	Brain swelling and extradural hematoma. Died 6th postop. day
12.	57 F	Glioblastoma, lt. parietal	Extirpation	1 hr., 25 min.	30.2 (86.4)	27.0 (80.6)	65	3 hrs., 5 min.	5 hrs., 15 min.	
13.	68 M	Astrocytoma, lt. parietal	Extirpation	2 hrs., 45 min.	29.9 (85.8)	25.0 (77.0)	65	2 hrs., 30 min.	7 hrs., 30 min.	
14.	65 F	Convexity meningioma, lt. parietal	Extirpation	2 hrs.	30.0 (86.0)	25.8 (78.4)	90	3 hrs.	3 hrs., 40 min.	
15.	44 M	Glioblastoma, lt. temporal	Partial extirpation	2 hrs.	30.0 (86.0)	25.2 (77.4)	60	3 hrs., 40 min.	4 hrs.	
16.	49 F	Acoustic neurinoma, rt. side	Radical extirpation; preservation facial nerve	2 hrs.	30.0 (86.0)	25.2 (77.4)	70	5 hrs., 35 min.	7 hrs., 15 min.	Bronchopneumonia
17.	53 M	Arteriovenous aneurysm, rt. parietal	Extirpation	3 hrs., 15 min.	30.0 (86.0)	26.0 (78.8)	65	4 hrs., 25 min.	7 hrs., 15 min.	
18.	40 F	Glioblastoma, rt. frontal	Extirpation	2 hrs.	30.0 (86.0)	25.7 (78.3)	65	4 hrs., 15 min.	2 hrs., 30 min.	Postop. intracerebral hematoma (evacuated). Probably damage to brain stem

corded in most cases. These abnormalities regularly disappeared during rewarming.

In Case 16 bronchopneumonia and fever developed on the 3rd day after operation and persisted for 3 days. This complication was probably ascribable in part to the lateral position of the patient during a fairly time-consuming operation (radical removal of an acoustic neurinoma with preservation of the facial nerve).

No symptoms or signs of prolonged renal complications were observed (only the nonprotein nitrogen and the daily urinary output were determined routinely). In analogy with what was observed by Andersen and Nielsen[1] in rabbits, the excretion of urine decreased considerably or almost ceased during hypothermia, to increase again during restoration of body temperature. In 1 patient (Case 10) urinary excretion was almost or completely suppressed for about 12 hours after the end of the operation, but without any accompanying increase in the nonprotein nitrogen. In this case the blood pressure had been lowered with Arfonad from 80 mm. Hg to 30–40 mm. Hg for about 45 minutes.

Though measures were usually not taken to protect the peripheral parts of the body, none of the patients showed any signs of superficial frostbite or pressure gangrene. The healing of the scalp wounds was uncomplicated in all cases.

Cerebral Complications. In 2 cases a postoperative hematoma was evacuated. In one of these (Case 11) the hematoma was caused by a silver clip having slipped off a dural artery; in the other (Case 18) it was not possible to ascertain the source of hemorrhage. Apart from these 2 cases and Case 10, we had the impression that, as far as cerebral symptoms in general are concerned, the postoperative course was usually smoother than what might have been expected without the use of hypothermia. No statistical data are available in support of this impression, but the following observations might be mentioned. As a rule, the patients were mentally clear the day after the operation. Three patients were out of bed sitting in a chair on the 2nd day after operation, 5 on the 3rd, and 4 on the 4th. On the average the patients were out of bed on the 4th postoperative day. The early postoperative rise in temperature was moderate, and no late fever reactions with or without signs of meningeal irritation were seen during the later postoperative course.

Blood Pressure and Bleeding. The fall and rise of the blood pressure followed a fairly uniform pattern during the different phases of the procedure of hypothermia (Fig. 3). In all 12 cases, where the lowest rectal temperature was 26.0°C. (78.8°F.) or less, a drop in blood pressure of about 50 per cent was recorded, and in 6 of these cases the blood-pressure level lay below 60 mm. Hg. In the remaining 6 cases there was a 50 per cent decrease in 3 and a level under 60 mm. Hg in only 1. In 2 cases (Nos. 8 and 10) the blood pressure was lowered further by the administration of Arfonad (Fig. 3): in Case 8 from 80–90 mm. Hg to 40–50 mm. Hg; in Case 10 from 70–80 mm. Hg to 30–40 mm. Hg. Apart from the aforementioned transient anuria, the administration of Arfonad was not followed by any demonstrable side effects.

18.	40 F	Glioblastoma, rt. frontal	Extirpation	2 hrs.	30.0 (86.0)	25.7 (78.3)	65	4 hrs., 15 min.	2 hrs., 30 min.	Postop. intracerebral hematoma (evacuated). Probably damage to brain stem

At all operations except 1 (Case 7) bleeding was only slight and hardly disturbing. The operative field could easily be kept entirely visible, and in most cases hemostasis presented no difficulties. The effect of the low blood pressure and decreased blood flow was particularly favourable in cases of intracranial aneurysms and richly vascularized gliomata. In 4 cases the control of venous bleeding from the dura mater was somewhat more troublesome than usual. This was obviously caused by a decrease of the coagulability and not by any high pressure in the cerebral veins.

Increased Intracranial Pressure and Swelling of the Brain. No measurements were made of the intracranial pressure during hypothermia. Of the 14 patients with cerebral tumour, 8 had papilledema, which was advanced in 5 and moderate in 3. Of these patients with papilledema, 3 were profoundly somnolent and 3 moderately so. At all operations for tumours, the gyri were found to be flattened, suggesting that the intracranial pressure had been raised for some time before the operation. When the dura mater was exposed at a rectal temperature of about 28.0°C. (82.4°F.) it regularly appeared to be less tense than what is generally seen in the presence of brain tumour with increased intracranial pressure. In 3 cases the dura mater was slightly tense; in the remainder it was, if anything, flaccid. The dura mater was always opened without previous ventricular puncture and neither immediately nor later during the operation did the brain bulge out through the defect. In those cases in which a glioma or a metastatic tumour was removed from the depth of a cerebral hemisphere, the wound in the brain was open and could be visually inspected until the very end of the operation. In all cases the dura mater was sutured without disturbing tension, and the rest of the wound was closed without decompressive measures. Thus, on no occasion did acute swelling of the brain occur during the operation.

DISCUSSION

Though no measurements were made of the intracranial pressure in these series, our observations at the operating table might be regarded as sufficiently conclusive to establish that lowering of the body temperature to 25°–27°C. (77°–80.6°F.) appreciably diminishes the increased intracranial pressure caused by brain tumours and mitigates the risk of acute swelling of the brain during intracranial operations. This implies a better approach to, and view of, the operative field as well as less traumatisation of the brain, and it also facilitates adequate closing of the wound. We offer no explanation for the underlying mechanism of this effect of hypothermia, but we suppose that it is the combined result of several factors including decreased blood pressure and blood flow, better oxygenation of the brain tissue, and possibly also a decreased production of cerebrospinal fluid. Neither do we know the minimum decrease in body temperature necessary to secure these surgical advantages, but even at 29.0°C. (84.2°F.) we observed a marked effect in 1 case.

Diminution of the bleeding at operation on richly vascularized tumours

proved valuable, but the greatest direct advantage of the low blood pressure and blood flow was observed in operations on vascular malformations, for the treatment of which deep hypothermia might open new surgical possibilities. Judging by observations made in our cases, this favourable effect of hypothermia is generally not optimal until the blood pressure has dropped below 60 mm. Hg, a level usually not reached until the temperature has fallen to below 27.0°C. (80.6°F.). Hypothermia in combination with ganglionic block was tried in 2 cases of intracranial arterial aneurysms. The fall in blood pressure obtained thereby (down to 30–50 mm. Hg) produced unusually favourable conditions for dissection of the aneurysm and neighbouring arteries. From what is known about oxygen transport and utilization at low body temperatures, it seems probable that lowering the blood pressure from 80 to 40 mm. Hg at 25°C. (77°F.) involves less risk than does lowering it from 120 to 60 mm. Hg at a normal body temperature, above all if cerebrovascular dynamics are deranged by increased intracranial pressure. Dundee *et al.*[10] have reported good results of a combination of medium deep hypothermia (30°–32°C.) and the administration of Arfonad by which method they obtained blood-pressure levels between 60 and 70 mm. Hg.

The suggested rôle of hypothermia in diminishing the frequency of lesions caused by local hypoxia cannot be evaluated on the basis of the present investigations. Transient occlusion of a major brain artery under hypothermia is an expedient to facilitate surgical treatment of intracranial vascular malformations. In none of our cases was this procedure indicated.

Our experience with the method for inducing hypothermia used in the present study was promising. We cannot confirm the opinion of Bailey *et al.*[2] that the use of cold circulating air is unsuitable because of the risk of cold injuries to the skin. Our decision to use inhalation anesthesia was based on the assumption that the diffusion processes dominating the transport of gaseous anesthetics are influenced less by low temperature than the processes responsible for breaking down anesthetics administered parenterally. Several of our patients still breathed spontaneously at rectal temperatures of 25.0°–26.0°C. (77.0°–78.8°F.). This observation is not in accordance with the opinion of Keown *et al.*[13] and others that respiration ceases below 28°C.

The induction of deep hypothermia is a major undertaking, which still involves certain risks. Is it nevertheless justifiable to use deep hypothermia in neurosurgery? Our experience suggests that the risks are not so great as to contraindicate its use in selected cases in which control of hemorrhage and brain swelling are imperative for the success of a hazardous operative procedure such as the extirpation of certain less readily accessible or highly vascularized tumours and very large arteriovenous aneurysms. But as yet we know too little about the untoward side effects of hypothermia, especially about ventricular fibrillation and how to prevent it, to advocate a more general use of deep hypothermia in intracranial surgery. If, however, future investigation can show that the risks are not significantly greater than those involved by the anesthetic methods now used in neurosurgery, deep hypo-

thermia might prove a valuable adjuvant in many intracranial operations: it will improve the results and decrease the strain on the neurosurgeon and perhaps permit operations now usually regarded as too risky, such as intracranial ligature of ruptured aneurysms in the acute stage.

SUMMARY

1. Eighteen major intracranial operations were done under general hypothermia with a lowest rectal temperature of between 24.8°C. (76.6°F.) and 29.2°C. (84.6°F.). The series included 14 cases of brain tumour and 4 cases of vascular malformation.

2. Hypothermia was induced and body temperature was restored by means of circulating air in a specially constructed apparatus.

3. There were 2 deaths, 1 caused by multiple cerebral metastases from a generally metastasizing bronchial cancer and 1 caused by a diffuse purulent meningo-encephalitis of unknown origin. Apart from bronchopneumonia of moderate severity in 1 case there were no extracerebral complications of any significance. Two postoperative hematomas were evacuated. There were no signs of cerebral complication ascribable to hypothermia.

4. Blood-pressure levels between 40 and 60 mm. Hg were recorded in 8 cases and between 60 and 90 mm. Hg in 10 cases. In 2 cases of arterial aneurysm an additional decrease in blood pressure to between 30 and 50 mm. Hg was induced by means of Arfonad. At these blood-pressure levels the conditions with regard to bleeding, hemostasis and dissection of aneurysms were highly favourable.

5. In the cases of brain tumour, observations during the operations showed that the preoperatively increased intracranial pressure was considerably reduced during the state of deep hypothermia. In none of these cases was a tendency to acute swelling of the brain observed during operation.

6. It is concluded that deep hypothermia produces certain favourable effects in intracranial surgery for brain tumours and vascular malformations, and that it should be used in *selected* cases in which these effects are of special importance.

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"POLYCYTHEMIA" ASSOCIATED WITH CEREBELLAR HEMANGIOBLASTOMA

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In 1943, Carpenter and co-workers[3] reported 2 cases of cerebellar hemangioblastoma with associated "polycythemia vera." They added 3 cases from the literature. Since then, about 22 such cases have been reported in the American literature.[3,4,8,12,21,25] Hemangioblastomas of the posterior fossa constitute only 2 per cent of intracranial tumors[5,6,16] and those associated with "polycythemia" less than 20 per cent of the total number of hemangioblastomas.[4] Thus, the association of "polycythemia" with posterior fossa hemangioblastoma is, to paraphrase Carpenter, an event of the greatest rarity.

Polycythemia rubra vera has been defined as a disease of unknown etiology, characterized by an excessive production of all marrow elements with resultant increase in red blood cell count, total red blood cell volume, white blood cell and platelet counts, and accompanied by increased blood viscosity and decreased velocity of blood flow.[19,23] Since quantitative blood studies have been done in only 1 of the reported cases of cerebellar hemangioblastoma,[3] it is difficult to determine whether polycythemia vera (as defined above) did, in fact, exist in the remainder. Possibly erythrocytosis, in which the red blood cell count is elevated with no increase in white blood cells or platelets, might be a more appropriate term to use.

We have recently studied 2 patients who had posterior fossa hemangioblastomas with associated erythrocytosis. Both patients were treated surgically, one with subtotal and the other with total removal of the tumor. We believe that the hematologic studies made in these 2 cases are more nearly complete than those reported heretofore.

It has not yet been proved that the relationship between the altered blood picture and the tumor is more than fortuitous. Although the basic physiopathology is unknown, the reduction in the degree of erythrocytosis in some cases following removal of the tumor suggests a cause-effect relationship. We hope that the cases here reported will yield some clue to the mechanisms involved.

CLINICAL DATA

Case 1. W.D., a 45-year-old white male, was admitted to the neurosurgery service on Nov. 3, 1952.

While in the Army in 1941, the development of signs of increased intracranial

pressure and cerebellar dysfunction led to a diagnosis of cerebellar tumor. Ventriculography revealed an "internal hydrocephalus" and was followed by suboccipital craniectomy. No gross tumor was found. Following operation, the patient was relieved of his symptoms for 3 years. Symptoms recurred in 1946 and he then received 2000 r of x-ray therapy to the posterior fossa.

He was next seen in another hospital in 1947 with no change in his clinical picture but with a red blood cell count of 5.38 million. One year later he was re-admitted to that hospital with progression of his signs of cerebellar dysfunction and with a red blood cell count of 6.5 million. He was seen intermittently in the outpatient department until 1949. His discharge note read, "The Tumor Board feels that there is a question of this man ever having had a tumor."

A rapid increase in his neurological deficits prompted admission to this hospital on Nov. 3, 1952.

Examination. The physical findings supported a diagnosis of cerebellar neoplasm. Lumbar puncture yielded clear, colorless fluid under a pressure of 264 mm. of cerebrospinal fluid. There were no cells; protein was 88 mg. per cent. Vertebral angiography revealed a diffuse vascularity of the posterior fossa suggestive of a vascular neoplasm. (Hematologic studies are reported in a later section.)

Operation. On Nov. 19, 1952, a posterior fossa exploration was carried out. An extensive meningocele was encountered on the right and there were three smaller separate ones on the left. Upon exposure of the cerebellum, a large extremely vascular tumor was occupying most of the posterior fossa and involving virtually the entire right cerebellar hemisphere. The neoplasm was gray and had numerous large tortuous venous and arterial channels whose major supply was not identified. Approximately one-third of the tumor was excised from the inferior and lateral portions of the exposed mass.

Postoperative Course. The patient exhibited no over-all improvement in his neurological deficits. He was discharged to a nursing home on Feb. 19, 1953.

On April 2, 1953, he was returned to the hospital because of sudden coma. Despite frequent periods of apnea, he responded to therapeutic efforts and was awake within 2 hours. However, from this point he deteriorated rapidly and died on the following morning. Cause of death was reported as aspiration pneumonia.

Autopsy. The fresh brain showed a moderate amount of thin bloody subtentorial fluid. There was a firm irregular mass occupying the right cerebellar lobe and a number of large tortuous veins along the right side of the brain stem and pons emerged from the mass. The remainder of the brain was grossly normal except for slight flattening of gyri and narrowing of sulci.

After fixation, the neoplasm was found to occupy almost the entire right cerebellar hemisphere. Some entering veins measured 4 to 5 mm. in diameter. On cut section, the most striking feature was the number of large vascular channels. The tumor was an admixture of grayish-white and reddish-brown tissue with scattered yellow foci, these latter presumably being xanthomas of "foam cells."

The microscopic picture was likewise characterized by striking vascularity. There were many thin-walled vessels of irregular shape with numerous sinusoids and venous lakes. The stroma showed two dominant characteristics—an amorphous eosinophilic matrix and packed masses of foam cells. Pathologic diagnosis: hemangioblastoma (Fig. 1).

Case 2. P.V., a 32-year-old white male, was admitted to the medical service on April 10, 1952.

The patient had experienced 2 months of vertigo and when seen by a private physician had a hemoglobin of 20.3 gm., hematocrit 64 per cent, red blood cells 9.52 million, and white blood cells 12,250. Following four blood donations, these studies were repeated at which time his hemoglobin was 15.6 gm., and red blood cell count 5.61 million. With the development of nausea and vomiting, he was sent to this hospital, where an additional history of progressive occipital headaches was elicited.

Examination. Roentgenograms of the skull were normal. Lumbar puncture revealed clear, colorless fluid under a pressure of 290 mm. of water, containing 61 mg. per cent of protein.

When seen in consultation on July 11, 1952, he had bilateral papilledema of 2 D. and bilateral nystagmus. (Hematologic studies are reported in a later section.)

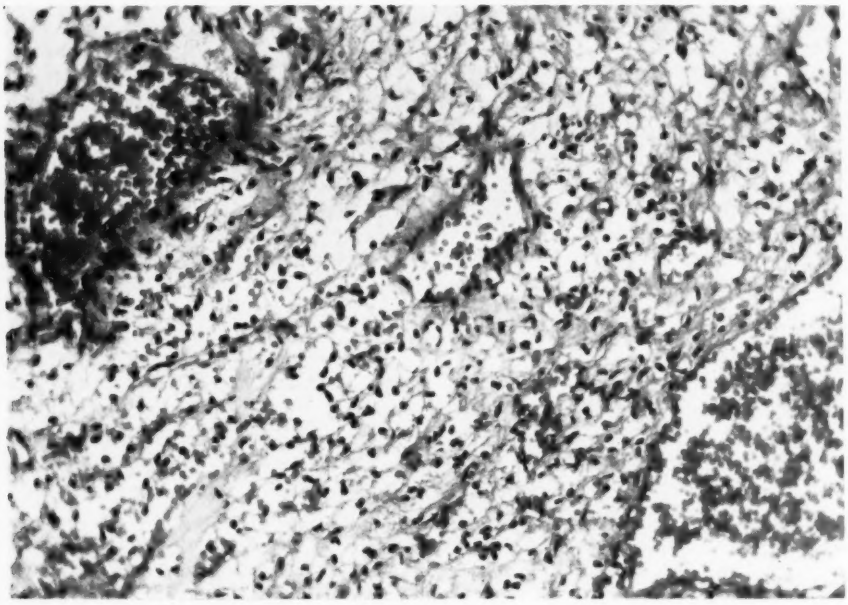

FIG. 1. *Case 1.* Microscopic appearance of tumor. Hematoxylin and eosin stain, ×240.

Operation. On July 16, 1952, ventriculography and suboccipital craniectomy were done. Ventriculography showed a grossly dilated ventricular system including 3rd ventricle and aqueduct. The aqueduct was occluded in its lower portion in a spindle-shaped manner, being displaced forward and to the right. At operation, an egg-shaped mass was found within the 4th ventricle, lying on the dorsal surface of the medulla and extending down to the level of C1. It had separated the cerebellar tonsils and pushed them superiorly and dorsally. The mass extended slightly to the left of the midline and well up into the 4th ventricle. The tumor was adherent to the floor of the 4th ventricle and the dorsal surface of the medulla and overlying cerebellum. It was dark red with many exceedingly large vessels on the surface. The blood contained in the vessels was all bright red. There were multiple vessels feeding the tumor, but the largest source of supply seemed to be from the region of

the left inferior cerebellar peduncle. Complete removal of the tumor was accomplished.

Postoperative Course. In the 2nd week after operation fever, stiff neck, and lethargy developed. A cyst over the operative site had appeared, but evacuation showed it was sterile and apparently produced by retained necrotic tissue. The lethargy responded in dramatic fashion to anticholinergic therapy and an uneventful physical convalescence followed. Behavioral difficulties necessitated the patient's transfer to the psychiatric service, from which he was discharged on Dec. 19, 1952.

At 1 year after operation, persisting cerebellar dysfunction could be elicited only on careful neurological examination.

Pathology. On cut section the surgical specimen showed innumerable small and

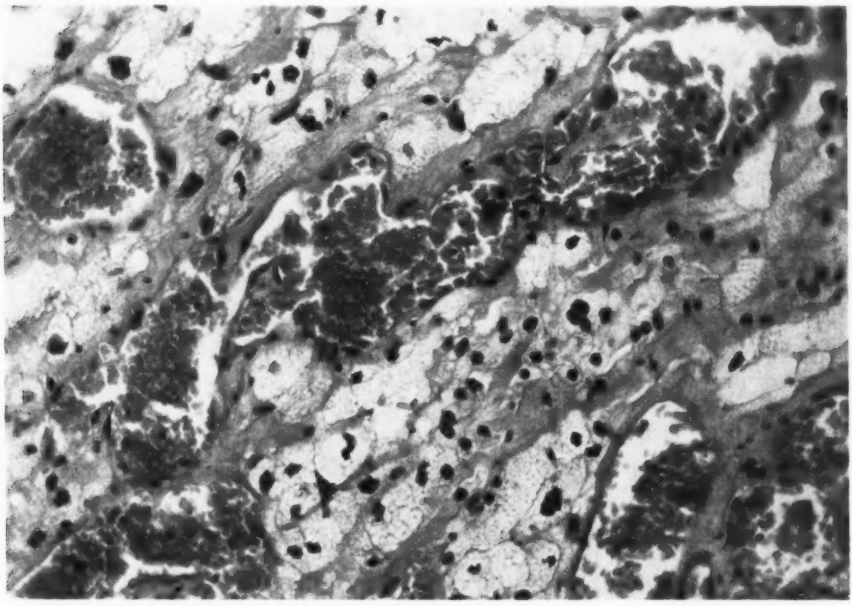

FIG. 2. *Case 2.* Microscopic appearance of tumor. Hematoxylin and eosin stain, ×240.

large vascular spaces. The surface of the nodule contained vessels as large as 0.5 cm. in diameter. There was a central cavernous space which appeared to communicate with other surface vessels.

Microscopic section showed an admixture of large vascular channels, some of which had thin walls as though representing veins, and others with rather dense, compact muscular walls suggesting arterial origin. Between these larger channels were compact areas of proliferating young capillaries. In addition, a moderate number of large vacuolated cells were seen suggestive of xanthoma cells. This composite picture was characteristic of hemangioblastoma (Fig. 2).

HEMATOLOGIC STUDIES

Adequate study of the blood picture in a patient with hematological

abnormalities requires more than a routine peripheral blood count. In an effort to study these cases as completely as possible, a number of determinations utilizing a variety of techniques were done.

Peripheral blood counts were done frequently. Each patient had a total of 18 preoperative peripheral counts which included red blood cells, hemoglobin, hematocrit, white blood cells, bleeding time, clotting time, prothrombin time, platelet count and reticulocyte count. Sternal marrow examinations were done. Determinations of the arterial oxygen content, capacity and concentration were carried out in Case 1. The mean corpuscular values were also calculated. Unfortunately these latter two studies were not performed in Case 2.

Blood-volume studies were carried out in both cases utilizing three techniques. The I^{131} method is a plasma dilution method using tagged serum. Both Cr^{51} and P^{32} methods involve the use of tagged red blood cells which

TABLE 1

Case 1. Peripheral blood counts
(18 preoperative counts; 10 postoperative counts)

	Red Blood Cells (million)		Hemoglobin (gm.)		Hematocrit (per cent)		White Blood Cells		Platelets (thousand)	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.
High	7.09	6.57	21.7	18.2	66	57	9,300	8,100	310	235
Low	5.77	5.32	18.2	16.5	59	52	7,700	5,500	167	325
Average	6.40	5.93	20.1	17.5	61	55	8,340	6,700	215	235
Normal	6.0		15		45		6,000–10,000		150–500	

are injected and later recovered in a blood sample and the red blood cell mass is calculated from these.[15] The Cr^{51} and P^{32} methods are immediately comparable, agreeing within 1 per cent or less.[7] The I^{131} method, on the other hand, generally gives values that are 5 per cent or more higher than the other two methods. For this reason, the I^{131} values are ignored in evaluating the results.

Table 1 is a summary of the pre- and postoperative peripheral blood counts in Case 1. It will be noted that the only abnormalities are in the erythrocytes and that these values (red blood cells, hemoglobin, and hematocrit) are reduced to nearly normal limits following operation. None of the postoperative figures is the result of blood depletion since continuous and adequate replacement was carried out during operation in each case.

Bleeding, clotting, and prothrombin times and reticulocyte counts were normal. Arterial oxygen content, capacity and concentration of Case 1 were likewise normal. Examination of the sternal marrow revealed hyperplasia of moderate degree involving both erythrocytic and myelocytic series.

Table 2 compares pre- and postoperative blood-volume determinations in Case 1. The principal preoperative abnormality is again in the erythro-

TABLE 2

Case 1. Blood volume determinations

	Preoperative		Postoperative	Normal
Method	I^{131}	Cr^{51}	Cr^{51}	Cr^{51}
Average hematocrit	62.5%	59%	47.3%	45.5%
Blood volume	10,026 cc.	5,550 cc.	4,450 cc.	4,960 cc.
Packed cell volume	6,266 cc.	3,275 cc.	2,450 cc.	2,326 cc.
Plasma volume	3,760 cc.	2,275 cc.	2,000 cc.	1,634 cc.

TABLE 3

Case 2. Peripheral blood counts
(18 preoperative counts; 32 postoperative counts)

	Red Blood Cells (million)		Hemoglobin (gm.)		Hematocrit (per cent)		White Blood Cells		Platelets (thousand)	
	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop.	Preop.	Postop
High	7.95	6.30	19.4	15.8	63	51	13,900	9,700	272	
Low	5.29	4.62	15.3	13.2	49	40	6,100	7,500	142	
Average	6.36	5.34	17.6	14.8	56	46.8	9,640	8,515	249	
Normal	6.0		15		45		6,000–10,000		150–500	

TABLE 4

Case 2. Blood volume determinations

	Preoperative		Postoperative			Normal
Method	P^{32}	P^{32}	P^{32}	Cr^{51}	Cr^{51}	Cr^{51}; P^{32}
Average hematocrit	52.5%	59.6%	55%	49%	50%	45.5%
Blood volume	4,777 cc.	3,798 cc.	4,090 cc.	3,150 cc.	3,140 cc.	4,960 cc.
Packed cell volume	2,508 cc.	2,267 cc.	3,150 cc.	1,550 cc.	1,570 cc.	2,326 cc.
Plasma volume	2,269 cc.	1,531 cc.	3,140 cc.	1,600 cc.	1,570 cc.	1,634 cc.

TABLE 5

Postoperative reductions in blood values

	Percentage Reduction	
	Case 1	Case 2
Average red blood cells	7.4%	16.0%
Average hemoglobin	12.9%	10.3%
Average hematocrit (peripheral)	9.9%	16.4%
Blood volume	19.9%	19.3%
Packed cell volume	25.2%	25.0%
Plasma volume	12.1%	12.1%
Average hematocrit (isotope)	19.8%	8.4%

cytes, and the postoperative levels show a normal range. The normal cited here is an average of figures for males.[23]

Tables 3 and 4 give comparable data for Case 2. Once again the only abnormalities are in the erythrocytes, the preoperative elevation of red blood cell count, hemoglobin, hematocrit and blood-volume values being reduced to normal following operation. This patient's bleeding, clotting, prothrombin times and reticulocyte count were normal. The sternal marrow showed erythroid hyperplasia.

Table 5 compares the changes in the blood picture following tumor excision in both cases. Even though Case 2 had a complete tumor excision and Case 1 an incomplete tumor removal, the percentage reductions in the blood-volume values were almost identical for both cases while the postoperative reductions in peripheral counts were less marked.

DISCUSSION

Polycythemia rubra vera frequently causes symptomatology of the central nervous system. In fact Loman and Dameshek[14] stated that "in polycythemia vera, symptoms referable to the head greatly outrank in incidence those relating to any other bodily system." Sloan[22] reported in detail 4 cases of polycythemia with neurological symptoms. Lawrence *et al.*[13] found the most frequent symptoms of polycythemia to be headache, dizziness, and visual difficulties. These are often the symptoms of increased intracranial pressure. Hence, as Brockbank[2] pointed out, the differential diagnosis is often exceedingly difficult. In fact, some patients with polycythemia have in the past had fruitless explorations for brain tumor[3] while others with antecedent polycythemia have been found to have subdural hematoma,[8] parietal glioblastoma,[19] or metastatic carcinoma of the frontal lobe.[19] Oppenheimer[17] in 1929 reported the case of a patient with polycythemia vera who had a cerebellar medulloblastoma at autopsy and in whom the polycythemia was the only clinical finding. Still, the combination of brain tumor and polycythemia is a rare one.

Beginning with Carpenter *et al.*,[3] about 22 cases of posterior fossa hemangioblastomas associated with an increase in absolute red blood cell count have been reported in the American literature.[3,4,8,12,21,25] Far more cases of hemangioblastoma without increase in red blood cell count have been noted.[4–6,16,18,21,24] Although the incidence of this association is not known, it certainly occurs in less than 18 per cent of all cases of cerebellar hemangioblastoma.

The chief difficulty that arises in the evaluation of the published cases lies in the type of hematologic studies performed. The only case in which blood-volume studies were done was that reported by Carpenter *et al.*[3] This patient's preoperative and postoperative values were similar to ours. Carpenter's second patient as well as all the others reported had peripheral counts only. Cramer and Kimsey[4] discussed polycythemia in some of their cases, stating that in polycythemia the red blood cell count is above 5 million

for females and 6 million for males. Silver and Hennigar[21] and also Woolsey[25] similarly diagnosed polycythemia in the absence of any additional studies. As has been pointed out, polycythemia vera is a specific hematologic abnormality which none of the reported patients exhibited. On the other hand, they all had erythrocytosis.

The results of tumor removal in some of the reported patients had a dramatic effect on the red blood cell count. Both patients discussed by Carpenter *et al.*[3] had preoperative counts of 6.5 million red blood cells or higher with comparable values for hemoglobin and hematocrit. Following operation, each patient had basically normal blood cell counts. Cramer and Kimsey[4] noted an elevated red blood cell count in some of their patients who proved to have solid or vascular hemangioblastomas at operation. These blood values were reduced after tumor removal. Some of their patients with cystic hemangioblastomas had recurrences. Of these, 63 per cent had an elevated red blood cell count and at re-operation the tumor was found to be either solid or vascular. The blood values likewise were reduced in these cases following removal of the tumor. Woolsey's[25] patient had a normal red blood cell count after removal of a cerebellar cyst only, following which the count then rose to 7.89 million. Following re-operation for removal of an obvious hemangioblastoma, it fell to 4.75 million. Thus, removal of the tumor apparently causes a decrease in circulating red blood cells to normal or near-normal levels. This follows the removal of only the solid or vascular types of tumor.

Both cases here reported had solid hemangioblastomas. Case 1 exhibited a postoperative decrease of 7.4 per cent in red blood cell count, 12.9 per cent in hemoglobin, and 9.9 per cent in hematocrit, while comparable reductions for Case 2 were 16.0 per cent, 10.3 per cent and 16.4 per cent respectively. The percentage reductions in blood-volume determinations were more striking. There was a 25 per cent postoperative decrease in packed cell volume in each case, a 19 per cent reduction in blood volume, and plasma volume was decreased 12 per cent. The primary postoperative change was thus in the absolute number of erythrocytes.

It is evident that "polycythemia," as defined, is a misnomer in these cases. However, in common usage, "polycythemia" refers merely to an increase in red cell levels and thus is semantically justifiable in describing the blood picture in such patients. However, we prefer the term "erythrocytosis."

The cause for the apparent relationship between erythrocytosis and posterior fossa hemangioblastoma is unknown. Four alternative explanations have been offered:

a) An actual neurogenic focus for the regulation of erythropoiesis. Haynal and Graf[11] observed polycythemia in 10 patients who had dysfunction of the hypophysial-hypothalamic system. They postulated that in cases of posterior fossa tumor, hydrocephalus caused by obstruction of the 4th ventricle produces hypothalamic dysfunction by pressure. This view, although not

completely shared, was felt to be the most likely by Carpenter *et al.*[3] in 1943.

b) The presence of extramedullary erythropoietic centers. In Lindau's disease, the hemangiomata are not limited to the cerebellum. Tonning *et al.*[24] postulated that although the lesions seem to be attributable to a developmental defect, there must also be a persistent alteration in tissue reactivity because new lesions may develop throughout life. They feel that the lesions "represent a fundamental persistent lack of integration between blood vessels and parenchyma." The continued development of hemangiomata in such organs as liver or spleen would thus be the source of the increase in circulating red blood cells.

c) Erythropoietic centers are stimulated by a disturbance in oxygen balance in the circulating blood caused by arteriovenous shunts in the tumor.

d) The formation of erythroid elements in the tumor itself. Cramer and Kimsey[4] found that tissue culture of the tumor from one case suggested erythropoietic activity. Sabin[20] in 1917 described the production of vessels, plasma and red blood cells in the chick. The anatomical description of this developing tissue suggests the structure of the cavernous hemangioblastoma as described by Cushing and Bailey[6] who were unable to demonstrate red blood cell formation in their series. In the cases that they studied, they mentioned not one patient with increased red blood cell count.

There are valid objections to at least three of these views. Erythrocytosis has not been reported in association with the general group of intracranial tumors, nor with other posterior fossa tumors. Thus it would be difficult to implicate hydrocephalus with resultant pressure dysfunction of the hypothalamus. The possibility of extramedullary erythropoietic centers cannot be ruled out, but the disseminated lesions of Lindau's disease are usually associated with the cystic hemangiomata. It will be recalled that apparently only the solid tumors are associated with erythropoiesis. This explanation thus does not fit the clinical observations. The arteriovenous shunt postulate is also unsupported by the evidence. Patients with primary intracranial vascular anomalies in which such a shunt exists do not exhibit an associated erythremia. Lawrence and co-workers[13] stated that there is no known anoxic stimulant to polycythemia vera.

The altered blood picture seen in these cases appears to be associated with only the solid hemangioblastomas, never the cystic variety. When the cystic type undergoes a change to solid type, erythrocytosis may apparently then develop. Such a discrete association suggests that the two are causally related. If so, then production of red blood cells by the tumor is the only one of the four suggested explanations that is tenable.

Recent work by Borsook *et al.*,[1] Erslev,[9] and Grant and Root[10] postulates the existence of a hormonal factor which has the property of stimulating erythropoiesis. In the experimental animal serum may be secured which, when injected into another animal, results in overproduction of red blood cells.

It may be that some hemangioblastomas secrete such a hormonal factor

which exists in a sufficient concentration to stimulate erythropoiesis. If true, the removal of critical amounts of the tumor could decrease this hormone concentration below the point of erythropoietic stimulation with resultant decrease in blood counts. This explanation obviates the need for finding erythropoietic activity in the tumor itself. Thus cystic varieties of tumor would contain insufficient functioning secretory tissue to produce the necessary amount of hormone for overproduction of red blood cells. With a change to the solid state, the amount of secretory tissue increases and erythropoiesis increases.

We must await further experimental studies to prove this hypothesis that the erythrocytosis associated with cerebellar hemangioblastoma is secondary to an erythropoietic hormone secreted by the tumor.

SUMMARY AND CONCLUSIONS

1. Two cases of posterior fossa hemangioblastoma (solid type) with associated erythrocytosis are presented.

2. Pre- and postoperative peripheral blood counts and blood-volume determinations reveal that the increased red count, hemoglobin, and hematocrit are caused by an increase in erythrocytic elements only and that these values show a dramatic decrease following surgical removal of the tumor.

3. In view of these additional data, it would appear that previous patients reported as having polycythemia did, in fact, have only erythrocytosis.

4. It is postulated that the erythrocytosis associated with solid cerebellar hemangioblastomas may be secondary to an erythropoietic hormone secreted by these tumors.

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THE SURGICAL TREATMENT OF ARTERIOVENOUS MALFORMATIONS OF THE BRAIN

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THE methods used in the treatment of arteriovenous malformations of the brain have recently been summarized by Norlén,[7] who reported a series of 10 cases in which the lesion was totally excised. Falconer[3] and Bassett[2] have each reported several cases in which treatment consisted of occluding the arterial supply without excising the malformation. Jaeger[6] described a case in which he ligated the middle cerebral artery just distal to its origin from the carotid for a vascular malformation in the distribution of the middle cerebral. Occlusion of one or more afferent arteries was used by French and Peyton[4] in 3 patients with arteriovenous malformations in the region of the vein of Galen.

Between March 1953 and February 1955, 9 arteriovenous malformations of the brain were seen in the Department of Neurological Surgery at Walter Reed Army Hospital. Surgical treatment was performed in all cases and consisted of total removal in 6 with various other methods used in the remainder. All of these patients except 1 were examined postoperatively by carotid arteriography. The choice of the operative procedure varied depending upon several factors.

In 2 of our patients, treatment consisted of occluding a single afferent vessel supplying the lesion. Arteriographic study showed the vascular malformations in these patients to be deeply seated in the frontal and parietal lobes where surgical approach directed at complete excision of the lesion would have resulted in extensive destruction of brain tissue. The blood supply in each case was seen on the arteriograms as a single vessel readily accessible for ligation. In the parietal lobe malformation (Case 1), this vessel was the terminal portion of the pericallosal artery. After ligation of this vessel, the possibility of some blood supply from the posterior cerebral still remained. However, we felt that the malformation was sufficiently removed from the distribution of the posterior cerebral to make this very improbable. The postoperative carotid arteriograms showed no evidence of filling in the malformation. The frontal lobe lesion (Case 2) was supplied by a large branch of the callosal marginal artery, and the arteriograms, following liga-

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tion, showed slight mottling of contrast medium only in the late venous phase. This method of treatment appears in such selected cases to be effective and obviates or minimizes the destruction of brain tissue that would result from total removal.

Obstructive hydrocephalus is a common complication of arteriovenous malformations in the region of the third ventricle.[1] One such lesion (Case 9) was encountered in our series and the Torkildsen operation was used effectively in treatment. This particular patient presented a history of headache of 2 months' duration with no neurological abnormalities except for bilateral papilledema. The ventriculograms were sufficiently indicative of a colloid cyst of the third ventricle to warrant surgical exploration. No evidence of a cyst was found, but a pulsating vessel estimated to be 3 or 4 mm. in diameter was clearly visualized passing transverse to the long axis of the ventricle just posterior to the massa intermedia. The vessel was doubly clipped. We felt this to represent unequivocal evidence of an arteriovenous malformation with block of the third ventricle and/or aqueduct of Sylvius. There was no evidence of the malformation on the postoperative carotid arteriograms; we presumed the lesion to be in the distribution of the posterior cerebral artery. The papilledema had almost completely disappeared at the end of the second postoperative week. Vertebral arteriograms were not made. Gillingham[5] has reported treating an arteriovenous malformation of the midbrain with a ventriculocisternostomy.

In their series of 43 patients with arteriovenous malformations, 24 of whom were operated upon, Olivecrona and Riives[8] cited 5 cases in which the external carotids were greatly dilated. They believed operative treatment was particularly hazardous when the external carotid contributed to the malformation. We encountered one particularly unusual case (Case 8) in which there were bilateral parietal lobe malformations in the parasagittal area, with the major portion of the blood supply being derived from tremendously enlarged external carotid branches on either side. The latter vessels produced two 7- to 8 mm.-wide channels in the skull on either side. The intracranial lesion communicated through a small channel in the skull with a pulsating angioma of the scalp overlying the region of the sagittal sinus. The intracranial lesions were completely excised after the preliminary ligation of the external carotid arteries. We feel the latter is an important measure.

Total removal was performed when the malformation presented on the convexity of the cerebral hemispheres, or when the lesion was below the surface but was accessible through the cavity remaining after the evacuation of an intracerebral hematoma which was the result of hemorrhage from the malformation. Four of our cases fall into the latter category.

The following are summaries of our cases, together with preoperative and postoperative arteriograms. Unless otherwise noted, arteriograms were made with 35 per cent Diodrast injected percutaneously, using local anesthesia.

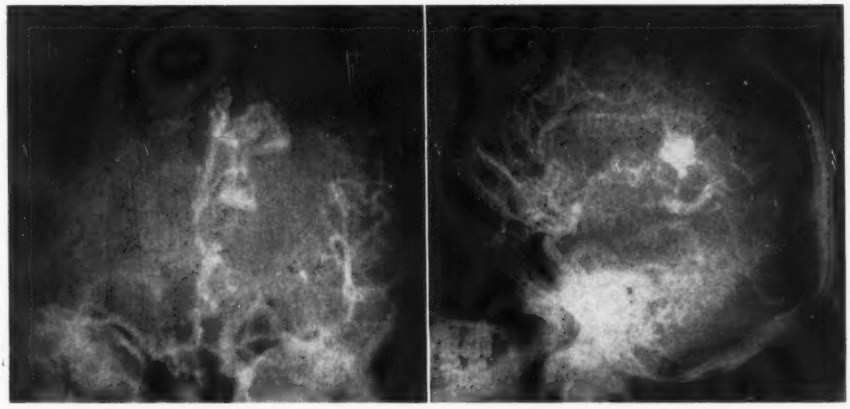
CASE SUMMARIES

Case 1. A 20-year-old man was admitted to Walter Reed Hospital on April 17, 1953, with a history of headache beginning on March 17 followed shortly by loss of consciousness which lasted 3 days. Spinal puncture revealed a pressure of 200 mm. with grossly bloody fluid. The patient continued to complain of mild headache.

Examination. The deep reflexes on the right side were slightly more active than on the left. Blood and urine were normal. Roentgenograms of the skull disclosed no abnormalities.

Left carotid arteriograms on April 2, 1953 revealed a large arteriovenous malformation arising from the left pericallosal artery and located over the splenium of the corpus callosum (Figs. 1 and 2). Drainage appeared to be through the vein of Galen and the straight sinus. On May 4, 1953, a right carotid arteriogram was made showing some Diodrast in the malformation which was obtained from collateral circulation through the anterior communicating artery.

1st Operation. On May 27, 1953, a left parietal craniotomy was performed with



FIGS. 1 and 2. *Case 1.* Anteroposterior and lateral preoperative arteriograms.

application of clips to the vessel which was felt to be the pericallosal just proximal to the malformation.

On the postoperative arteriograms the clips appeared just posterior to the malformation, probably on a branch from the posterior cerebral artery.

2nd Operation. On June 19, 1953 a slightly more anterior craniotomy was performed and several clips were applied to the pericallosal artery after the vessel was definitely identified.

Postoperative Course. The patient had slight numbness and weakness of the right hand which cleared completely within 2 weeks. Left percutaneous carotid arteriograms on June 30, 1953 showed the left pericallosal artery proximal to the clip (Fig. 3). The malformation was not visualized with contrast medium.

Case 2. A 16-year-old woman was admitted to Walter Reed Army Hospital Jan. 5, 1954. Four days earlier she had experienced a subarachnoid hemorrhage with loss of consciousness which lasted for approximately 24 to 36 hours. Upon regaining

consciousness she complained of severe frontal headache. A spinal puncture 3 days after the onset of symptoms revealed grossly bloody fluid with pressure of 300 mm.

Examination. The patient was drowsy but could be readily aroused. Her neck was moderately stiff and her left pupil was slightly larger than the right. There was a bilateral Babinski sign. Blood and urine were normal. Spinal fluid on January 6 contained 600 red blood cells per c.mm.

Left carotid arteriograms on January 6 showed, with contralateral compression

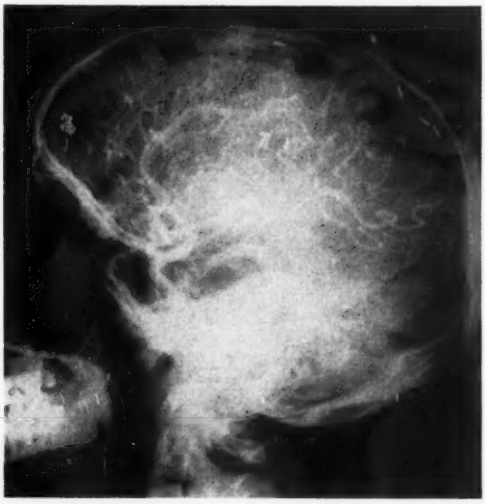
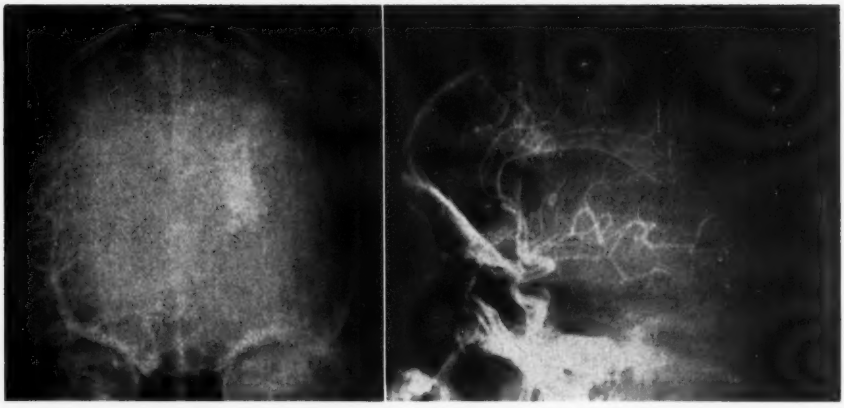


FIG. 3. *Case 1.* Lateral postoperative arteriogram.



FIGS. 4 and 5. *Case 2.* Anteroposterior and lateral preoperative arteriograms.

of the right common carotid artery, a vascular malformation in the right frontal lobe in the region near the tip of the right lateral ventricle (Figs. 4 and 5). A single artery passing from the right callosal marginal artery was feeding the malformation. The vessels on the left side of the brain appeared normal.

Operation. Right frontal craniotomy was performed on Jan. 7, 1954, and the afferent artery passing to the malformation was ligated.

Postoperative course was uncomplicated. A right carotid arteriogram on January 24 showed no evidence of contrast medium in the malformation other than a slight degree in the venous and capillary phase (Fig. 6). The patient was discharged on Jan. 28, 1954. The neurological findings were normal except for slight increase in the reflexes of the left upper and lower extremities. It was felt that the arterial blood supply to the malformation had been obliterated and that there was no longer any danger from further hemorrhage.

Case 3. A 36-year-old man was admitted to Walter Reed Army Hospital on Jan. 29, 1955, several hours after the onset of severe headache, left hemiparesis, and semicoma. A spinal puncture revealed grossly bloody fluid with pressure of 280 mm.

Examination. The patient was in semicoma and responded to painful stimuli with only a word or two. There were left hemiparesis and hypalgesia. His temperature was 100°F., and pulse rate was 92. White blood cell count was 18,500. There was a trace of albumin in the urine. The spinal fluid was xanthochromic and contained 35 cells, 95 per cent of which were lymphocytes.

Carotid arteriography was attempted on Feb. 2, 1955, but the arteriograms

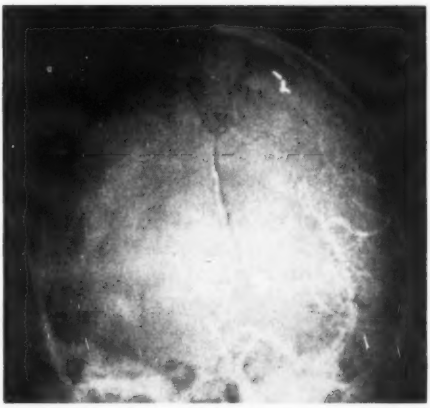
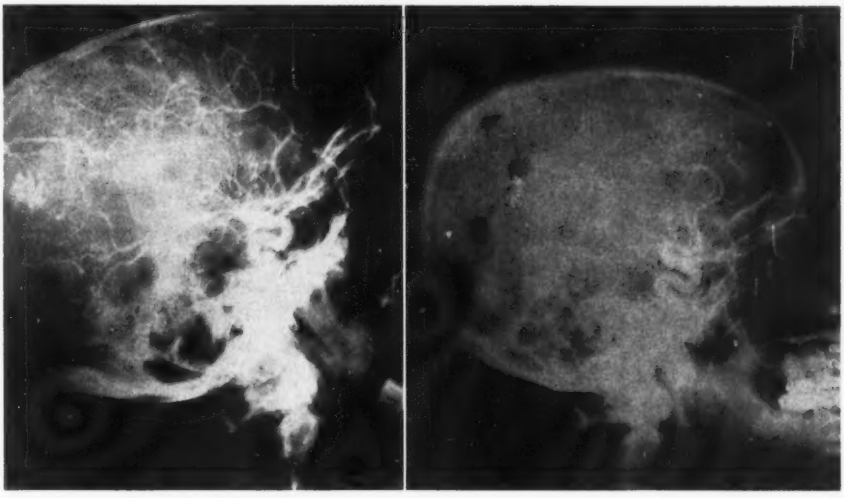


FIG. 6. *Case 2.* Anteroposterior postoperative arteriogram



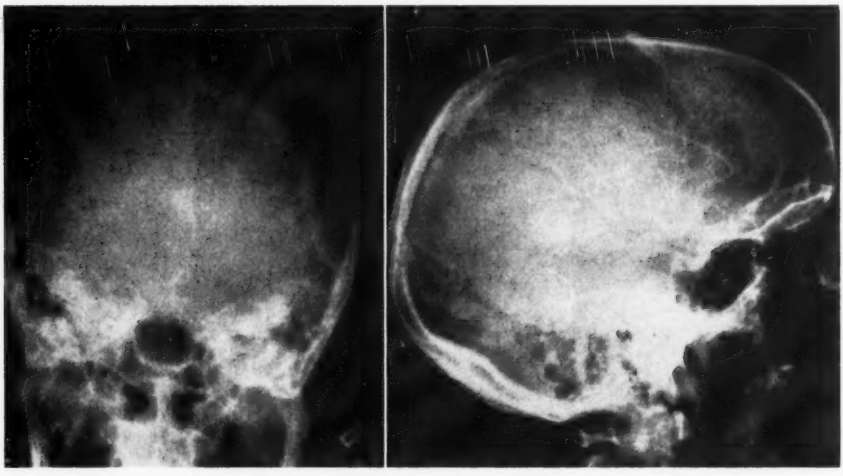
FIGS. 7 and 8. *Case 3.* Lateral preoperative and postoperative arteriograms.

were unsatisfactory because of the patient's movements. On February 3, using general anesthesia, a right percutaneous carotid arteriogram was made and a large vascular malformation was found at the terminal portion of the right pericallosal artery (Fig. 7).

Operation. A right parietal craniotomy was performed 1 to 2 hours after the arteriographic study. A large right parietal lobe hematoma was evacuated and the arteriovenous malformation was completely excised.

Course. The day after operation the patient was well oriented but drowsy. The left hemiplegia was markedly improved, particularly in the left upper extremity. On February 11, the patient was allowed to be in a wheel chair and by February 23 the strength and coordination of the left upper extremity had almost returned to normal. There was marked left-right confusion. By March 15, he was ambulatory. Arteriograms on April 29 showed good filling with no evidence of the malformation (Fig. 8) and he returned to limited duty on May 1. At the time of discharge there was weakness in the left lower extremity which was most pronounced in the peroneal musculature. Two-point and position sense of the left leg were only slightly impaired. He walked well with a foot-drop brace.

Case 4. A 29-year-old man was admitted to Walter Reed Army Hospital on July 17, 1954. Approximately 5 days earlier he had suffered sudden headache,



FIGS. 9 and 10. *Case 4.* Anteroposterior and lateral preoperative arteriograms.

blurring of vision, and dizziness. Shortly after noticing a defect in the right visual field he lost consciousness for several hours.

Examination. Spinal puncture revealed grossly bloody fluid. Left percutaneous carotid arteriograms on July 20 showed an arteriovenous malformation deep in the left parietal lobe (Figs. 9 and 10). This patient had had a left hemiplegia in 1941, which cleared over a period of several months.

Positive neurological findings were a right homonymous hemianopsia with moder-

ate ideational apraxia and alexia. The deep reflexes on the right side were more active than on the left. Blood and urine were normal.

Operation. On Sept. 3, 1954, a left parietal craniotomy revealed an old blood clot in the left parietal lobe which contained approximately 50 cc. of serous sanguineous fluid. In the region of the glomus of the choroid plexus an angiomatous malformation was found and completely excised.

Postoperative course was uncomplicated. By September 19, the patient was ambulatory. Arteriograms made on September 20 showed no evidence of the malformation (Fig. 11). At the time of his discharge from the Army he had a right homonymous hemianopsia and moderate alexia.

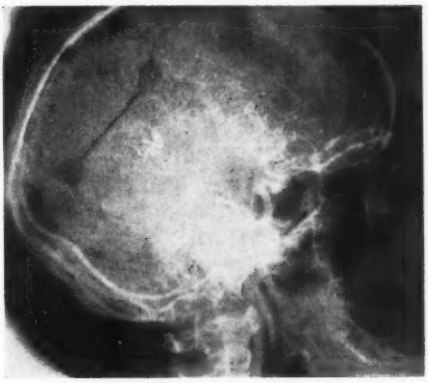


FIG. 11. *Case 4.* Lateral postoperative arteriogram.

Case 5. A 23-year-old male Negro was admitted to Walter Reed Army Hospital on Aug. 10, 1954. On July 13, 1954, headache had developed, with dizziness and confusion followed by loss of consciousness. Spinal puncture revealed grossly bloody fluid. He gradually regained consciousness over a 7-day period.

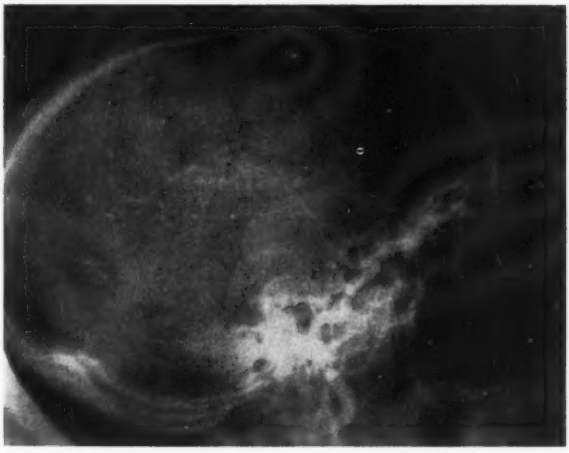


FIG. 12. *Case 5.* Lateral preoperative arteriogram.

Examination. There was marked weakness of the right upper and lower extremities and he had moderate motor aphasia. Blood and urine were normal.

Left carotid arteriograms on Aug. 24, 1954 were questionable. Arteriography was repeated on August 31 using the open technique, and a small vascular malforma-

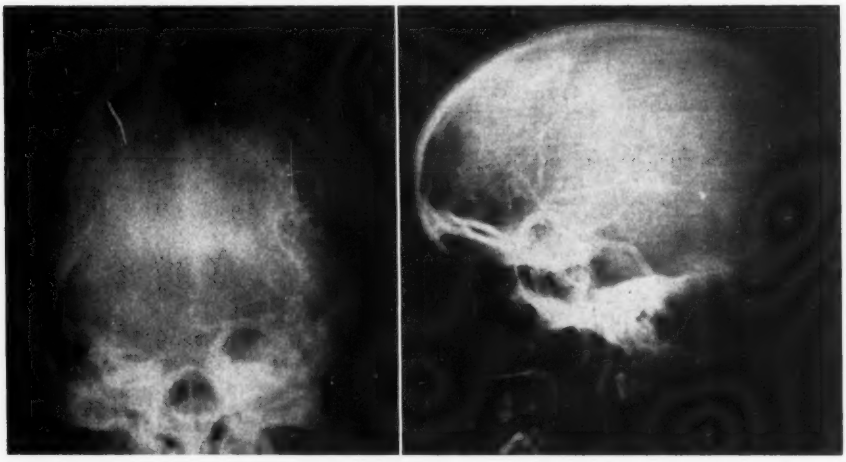
tion in the superior temporal branch of the left middle cerebral artery (Fig. 12) was found.

Operation. On Nov. 23, 1954, a left parietal craniotomy was performed and a cystic area, 3 to 4 cm. in diameter, in the posterior portion of the left temporal lobe was located. A small angiomatous malformation was encountered and completely excised.

Postoperative course was uneventful. On Jan. 3, 1955 the patient had only slight right hemiparesis and a mild expressive aphasia and he was discharged on Jan. 13, 1955.

Case 6. A 19-year-old woman was admitted to Walter Reed Hospital on Oct. 22, 1954. In March 1954, while 4½ months pregnant, she had experienced sudden left frontal headache with nausea and vomiting. Spinal puncture revealed grossly bloody fluid. Headache and mild confusion persisted for 2 weeks. She continued to have moderate pain in the left frontal area and below the left eye. Three weeks before admission she experienced a generalized convulsive seizure.

Examination. The patient had hypalgesia over the 2nd division of the left 5th



FIGS. 13 and 14. *Case 6.* Anteroposterior and lateral preoperative arteriograms.

nerve. The right side of her face showed a supranuclear paresis. The right biceps and triceps reflexes were slightly more active than the left. Blood and urine were normal. Roentgenograms of the skull were normal.

On Oct. 27, 1954 left carotid arteriography was attempted with the needle being inadvertently placed in the vertebral artery. With contralateral carotid compression, the posterior cerebral circulation, bilaterally, and the right carotid circulation were all visualized and appeared normal. A left carotid arteriogram was made the following day and a large arteriovenous malformation in the anterior aspect of the left temporal lobe was located (Figs. 13 and 14).

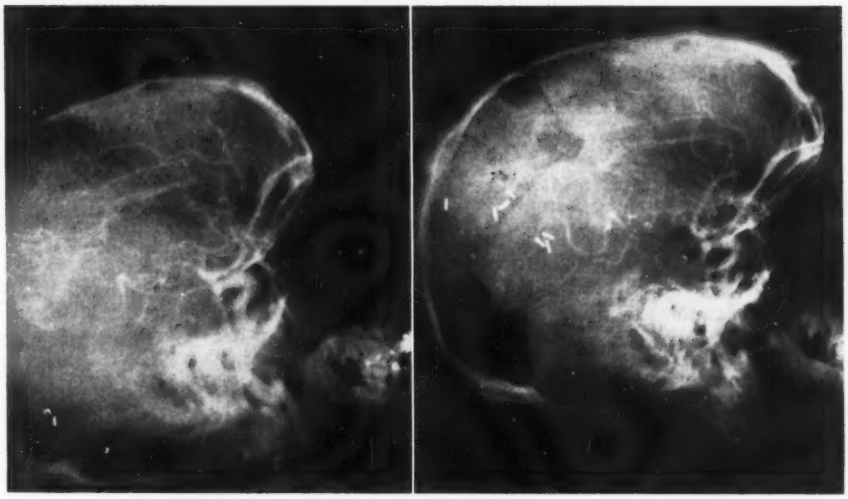
Operation. A left frontal temporal craniotomy was performed and the lesion was completely excised.

Postoperative course was uncomplicated with no paresis of the right arm or leg. There was some slight hesitancy in speech for a few days but this cleared completely.

FIG. 15. *Case 6.* Lateral postoperative arteriogram.

Arteriograms on Dec. 1, 1954 revealed the malformation to have been completely removed (Fig. 15) and the patient was discharged on Dec. 3, 1954.

Case 7. A 29-year-old woman was admitted to Walter Reed Army Hospital on March 29, 1954. On March 19 sudden pain had developed in the top of her head followed shortly by loss of consciousness. The spinal fluid was bloody and a physical examination at that time revealed a left hemiparesis. She remained unconscious for about 24 hours. At the time of admission she was asymptomatic except for a mild headache.



FIGS. 16 and 17. *Case 7.* Lateral preoperative and postoperative arteriograms.

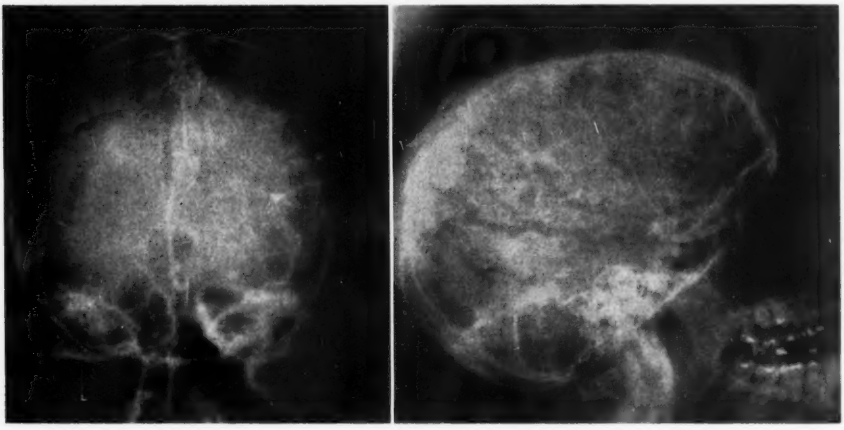
Examination. There were no neurological abnormalities except that reflexes of the right upper extremity were less active than the left. Blood and urine were normal. Roentgenograms of the skull were normal. Spinal fluid protein was 147 mg. per c.mm.

Carotid arteriograms on April 5, 1954 showed an arteriovenous malformation on the medial aspect of the right parietal lobe (Fig. 16).

Operation. Craniotomy on April 13, 1954 revealed a large hematoma in the right parietal lobe, on the medial aspect of which was an arteriovenous malformation. The latter was completely excised.

Postoperative course was uncomplicated. Arteriograms on April 28, 1954 showed the malformaton to have been completely excised (Fig. 17). Neurological findings were normal except for mild sensory impairment over the left upper extremity and the patient was discharged on May 3, 1954.

Case 8. A 34-year-old woman was admitted to Walter Reed Army Hospital on Jan. 26, 1955. Eight years previously she had noticed a roaring in her head synchronous with the heart beat. This persisted and increased somewhat in severity. In



FIGS. 18 and 19. *Case 8.* Anteroposterior and lateral preoperative arteriograms.

March, 1954, she had had a generalized convulsive seizure. Seizures occurred with increasing frequency following this, so that during December 1954 she was having one or two attacks daily. She was hospitalized at Ft. Campbell, Kentucky in the spring of 1954, where arteriograms showed an arteriovenous malformation, bilaterally, in the parietal lobes.

Examination. There was a loud bruit synchronous with the heart beat heard over all areas of the head but loudest in the region of the vertex. There was a pulsating mass 6 by 6 cm. over the posterior sagittal area of the head. The remainder of the neurological findings were normal. Blood and urine were normal. Roentgenograms of the skull revealed tremendously enlarged vascular channels of the middle meningeal artery, bilaterally. These converged on either side into the posterior sagittal area.

On Feb. 1, 1955, using general anesthesia and the open technique, bilateral internal carotid and bilateral external carotid arteriograms were made, and vascular malformations on either side in the posterior and medial aspect of the parietal lobes

were located (Figs. 18 and 19). The malformations were irrigated by both the internal and external carotid arteries on either side. The external carotid arteries were ligated shortly after the arteriographic study.

Operation. On Feb. 8, 1955, biparietal craniotomy was carried out. The branches of the middle meningeal arteries on either side were approximately 8 mm. in size and were deeply embedded in the calvarium. Upon reflection of the dura mater on either side of the sagittal sinus, several large vascular channels passing between the branches of the middle meningeal arteries and the underlying malformations were clipped and cauterized. The malformation on the left was some 4 cm. in diameter with several large vessels passing into the sagittal sinus. The one on the right was somewhat smaller. Both malformations were completely excised.

Postoperative course was uncomplicated. The patient had no more spells of lightheadedness nor syncope up to the time of her discharge from the hospital.

On Feb. 28, 1955, bilateral carotid arteriograms were made and the malformation

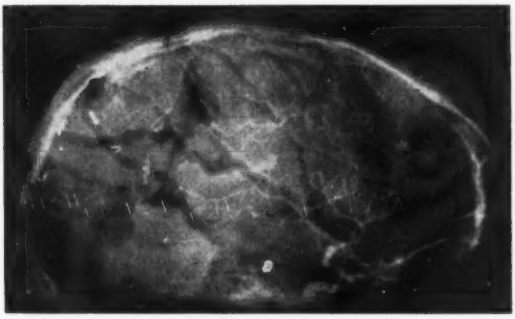


FIG. 20. *Case 8.* Lateral postoperative arteriogram.

was found to have been completely removed except for a slight pooling (3 mm. in diameter) of contrast medium in the left parietal area (Fig. 20). She was discharged on March 1, 1955 with no neurological abnormalities.

Case 9. A 23-year-old woman was admitted to Walter Reed Army Hospital on Sept. 18, 1954. She had experienced biparietal headaches all her life. Two months before admission there was a rapid onset of a severe throbbing headache with occasional nausea. Two weeks before admission she had noticed a blurring of vision.

Examination. There was papilledema of 3D. with several small linear hemorrhages in the left fundus. Visual fields showed enlargement of the blind spots. Blood and urine were normal. Roentgenograms of the skull disclosed no abnormalities.

1st Operation. On Sept. 23, 1954, ventriculography revealed marked symmetrical dilatation of the lateral ventricles with a filling defect in the posterior two-thirds of the third ventricle. A ventriculocisternostomy (Torkildsen) was performed on the same day.

2nd Operation. Because the ventriculograms indicated a colloid cyst of the third ventricle, exploration was carried out on Oct. 5, 1954. There was no evidence of a colloid cyst, but a large vessel, estimated to be 4 mm. in diameter, ran transverse to the long axis of the third ventricle in the region just posterior to the massa intermedia. Two clips were placed on the vessel.

Postoperative Course. The patient had a left hemiplegia after operation. On Oct. 14, 1954 she had definite movement of her left upper extremity and by the end of

another 10 days she had almost regained normal function of the left upper and lower extremities. With contralateral carotid compression, a left carotid arteriogram was made on Nov. 3, 1954 which revealed normal circulation from the internal carotid arteries. She had been free of headache since a few days after the last craniotomy and her previous papilledema had almost completely cleared. She was discharged on Nov. 10, 1954.

DISCUSSION

The clinical course of arteriovenous malformations of the brain has been well documented by Olivecrona and Riives. There is a relatively high incidence of gross subarachnoid hemorrhage and intracerebral hematoma with secondary hemiparesis. The importance of performing arteriographic study the first day on patients with gross subarachnoid hemorrhage and hemiparesis should be emphasized, since patients with an arteriovenous malformation, complicated by intracerebral hematoma, need early surgical treatment. Four of our patients had intracerebral hematoma formation, and the removal of the clot in one was an emergency measure. The 9 patients comprising this series have each been able to resume essentially the same activity as that engaged in before the onset of symptoms referable to the vascular malformation.

SUMMARY

1. Nine cases of arteriovenous malformations of the brain have been presented.

2. Treatment by ligation of a single afferent artery has been emphasized in 2 cases.

3. Ventriculocisternostomy (Torkildsen) was used in a patient with vascular malformation of the third ventricle.

4. Six arteriovenous malformations were totally excised.

5. Preliminary ligation of the external carotid arteries is advisable when these vessels contribute to the blood supply of an arteriovenous malformation.

6. Early arteriographic study should be carried out in suspected arteriovenous malformations, and in certain instances early surgical treatment is advisable.

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PINEALOMA WITH METASTASES IN THE CENTRAL NERVOUS SYSTEM

A RATIONALE OF TREATMENT*

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THE metastatic potentiality of pineal tumors has been demonstrated by a number of isolated case reports. In 1911, Bailey and Jelliffe[4] summarized the literature pertaining to pineal tumors since the first report by Blane in 1800. In none of these cases was the occurrence of metastatic spread mentioned. In 1925 Horrax and Bailey[19] reported 2 cases in which there were metastases and it has been shown subsequently that tumors arising from the pineal body may extend beyond their site of origin by direct continuity, by seeding through the cerebrospinal fluid pathways, and, occasionally, through the blood stream. These reports have been summarized in Table 1.

There are 3 reported cases of pineal tumors with extracranial metastases. Stowell *et al.*[32] described a patient with soft, nodular metastases in his lung. This patient had been subjected to a transcallosal exploration in an attempt to remove his tumor. It is of interest to note that this neoplasm was histologically identified as a chorionepithelioma, and the chorionic gonadotropin was elevated both in the urine and cerebrospinal fluid. Tompkins *et al.*[34] found metastases to the lung in 2 out of 13 cases of pineal tumors in which autopsy was performed. In 1 of their cases direct invasion of the straight sinus by the tumor was demonstrated. This patient had been explored through the right parieto-occipital cortex with incomplete removal of his lesion. He died 4 months postoperatively and pathologically this tumor was classified as a teratocarcinoma. In their second case the tumor was partially removed at surgery and was histologically identified as a pinealoma. This patient was given roentgen therapy to the posterior portion of the third ventricle. Ten months later a spastic paraplegia developed, and the cerebrospinal fluid at this time contained "fragments of necrotic tissue in which neoplastic cells were identified." Radiation was then given to the vertebral column, but the condition of the patient deteriorated and he died 6 months later. At autopsy tumor could not be identified at the site of the pineal body,

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and the structures in this region were replaced by arenaceous bodies and dense fibrous connective tissue. However, tumor was found in the lung and tracheobronchial lymph nodes. Examination of the spinal cord was not done. As will be noted, all reported patients with extracranial spread of their tumor had been subjected to direct surgical exploration. It is probable that this has played some part in allowing the malignant cells access to the blood stream.

Spread by means of the cerebrospinal fluid pathways has been mentioned by Cushing[9] who pointed out the similarity between the pinealoblastoma and the medulloblastoma stating that they are "akin . . . both in their microscopic appearance and behaviour (e.g., in their tendency to seed themselves in the floor of the third ventricle)." Horrax and Bailey[19] noted in their series of 12 cases that there was spread to the anterior part of the third ventricle or posterior fossa in 2. Russell and Sachs[30] reported that in 7 of 15 cases at autopsy there were metastases to either the ventricles or the subarachnoid space. Baggenstoss and Love[3] reported a patient from whom a tumor, which was identified pathologically as a pinealoma, was removed from the suprachiasmatic region. Roentgen therapy was given to the head and the patient did well for 18 months at which time he began to have pain in his left leg. At laminectomy multiple tumor nodules, having the same histologic appearance as his cranial lesion, were found to be implanted about the cauda equina.

The occurrence of spread of pineal body tumors is likely to be more frequent than may be inferred from the number of reported cases because of the lack of pathologic examinations of the spinal cord. It has been shown that examination for these metastases must be done histologically, as, on occasion, diffuse meningeal involvement that is not grossly obvious may occur.[11] It is also possible that before the use of palliative roentgen therapy, many of these patients died quite promptly with increased intracranial pressure as a result of their primary tumor, and thus metastases did not have time to occur or were not clinically significant prior to death. As the longevity of the patient is increased by decompression combined with roentgen treatment directed toward the primary lesion, an increased incidence of metastases may become apparent. The following cases are presented in the hope that a more general cognizance of this problem may lead to a more efficacious manner of therapy.

CASE REPORTS

Case 1. NCBH #185634. L.L., a 10-year-old white male, was admitted to the North Carolina Baptist Hospital on May 17, 1954. He had been in good health until 10 months previously, when his appetite became poor, he began to lose weight, and he seemed to tire more easily. He then began to have polydipsia and polyuria. Seven months before admission he started having frontal headaches and aching pains in his legs and was admitted to another hospital for metabolic investigation without any definite conclusions being reached. The patient became continually weaker, and began to have vomiting associated with his headaches. Studies done 3 months prior

to admission showed the cerebrospinal fluid to contain 65 leukocytes (72 per cent mononuclear cells); protein 21 mg. per cent, sugar 48 mg. per cent. During the next 2 months the patient became increasingly ataxic, and the vision in his right eye diminished. Because of his increasing neurologic deficit he was referred for further study.

Examination. The patient was cachectic and appeared chronically ill and malnourished. He had intermittent periods of drowsiness, and it was difficult to sustain his attention for more than a few minutes at a time. The head was $21\frac{3}{8}$ inches in circumference and there was prominence of the frontal bosses. He had bitemporal baldness. There was no Macewen's sign. There was moderate bilateral optic atrophy with a complete left temporal visual field loss and an incomplete right lower temporal field defect. Vision—O.D. 20/200; O.S. 20/50. Extraocular movements were normal. There was no ataxia of the extremities, but there was slight truncal ataxia. The

FIG. 1. *Case 1.* Ventriculogram, brow-down position. Note mass presenting in posterior portion of the third ventricle with dilatation of the lateral ventricles.

genitalia were small and left testis was undescended. There were no palpable testicular masses.

Laboratory Findings. Urinalysis and blood counts were normal. Blood test for syphilis was negative. Tuberculin test was negative. Spinal fluid: pressure 160 mm.; 134 leukocytes (98 per cent mononuclear cells); protein 85 mg. per cent; sugar 39 mg. per cent. Roentgenograms of the chest were negative, and skull films showed no evidence of calcification above the sella turcica or in the pineal region.

Hospital Course. The patient was prepared for 2 days with ACTH and cortisone because of the possibility of his having a suprasellar lesion, and on May 24, 1954 ventriculography was performed. This showed dilatation of the lateral ventricles and the anterior portion of the third ventricle. Air passed readily between the two lateral ventricles. In the brow-down position a mass was demonstrated in the posterior part of the third ventricle, and air did not pass beyond this point (Fig. 1).

Operation. The posterior fossa was explored with the intent of performing a ventriculocisternostomy. When the dura mater was opened, a pink-white fleshy

nodule was found adherent to the left cerebellar hemisphere. The fourth ventricle appeared to be completely normal. The lower end of the aqueduct of Sylvius was seen, and from it protruded a small tuft of tissue similar in appearance to that found on the cerebellum. The cerebellar nodule was quite superficial and easily removed. A soft #8 red rubber catheter was placed subcutaneously as a shunt between the right lateral ventricle and the cervical subarachnoid space and the wound was closed.

Postoperative course was uneventful, and the patient was continued on gradually decreasing doses of ACTH and cortisone for 7 days. He was discharged on his 11th postoperative day, and was referred to the Charlotte Memorial Hospital for roentgen

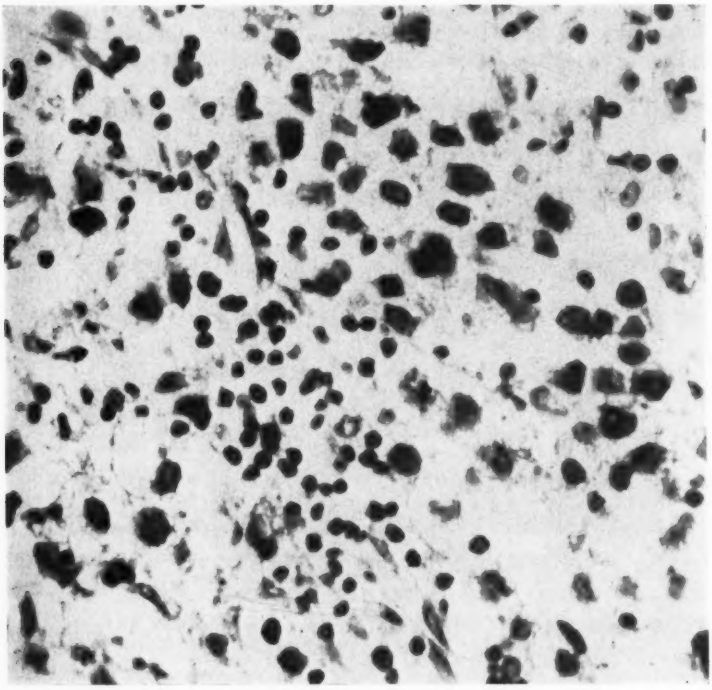


FIG. 2. *Case 1.* Photomicrograph of nodule removed from surface of left cerebellar hemisphere. Hematoxylin and eosin stain, ×660.

therapy with a recommendation for total cerebrospinal axis irradiation. Treatment was given with 220 kV.; 0.5 Cu, 1.0 Al filter. The patient received an air dose of 1800 r through each of 2 lateral ports directed to the region of the pineal body over a 12-day period. He also received an air dose of 1700 r through each of 4 ports covering the entire spinal column over a period of 18 days.

The patient has now been studied for a period of 12 months and has shown gradual improvement. He has gained 15 pounds, but is still drinking up to 1 gallon of fluids a day. His appetite is good and he is free from headache. He is no longer ataxic, and there are no other cerebellar signs. At present his vision is 20/70 in both eyes, but there is still a temporal defect in the visual field of his left eye.

Pathology. NCB No. 54-2086 (Fig. 2). Biopsy from cerebellar hemisphere. The tumor is composed of cells showing a gradation in nuclear size. The smaller cells are about the size of a lymphocyte and have scanty cytoplasms. There are some intermediate-sized cells and numerous cells with large, heavily staining nuclei. In some of these a nucleolus is visible. Mitotic figures are not seen. There is a finely reticulated background produced by the cytoplasmic processes of these cells. There is an occasional multinucleated giant cell. The vessels appear normal except for occasional perivascular clusters of the small cells. Diagnosis: Pinealoma.

Comment. This patient exemplifies the spread of pineal tumors by means of the cerebrospinal fluid to other parts of the central nervous system. The presence of cells in the spinal fluid is of interest as it seems likely that a certain number of these may have been derived from the tumor itself. There is a morphologic similarity between the small cells of pineal tumors and the mononuclear cells of hematogenous origin, and it is probable that on routine examination of the spinal fluid the significance of this pleocytosis may pass unrecognized. Dorothy Russell[29] considers the small cells as immature forms of the larger parenchymal cells, and hence the production of tumor implants from these cells seems quite plausible.

This patient also had evidence of injury to the structures in the suprasellar region. The early onset of diabetes insipidus in cases of pineal tumors has been noted by other authors.[16,33] This is occasionally caused by actual tumor implants in the anterior portion of the third ventricle, but it was felt that the ventriculogram adequately ruled out any significant mass in this location. It is more probable that these symptoms were secondary to the obstructive hydrocephalus with ballooning of the lamina terminalis into the suprasellar region. It was because of the possibility of a lesion in this area that the child was given supportive therapy with ACTH and cortisone, as has been recommended by Ingraham *et al.*[21] This may have been helpful in this debilitated child as he withstood air studies and operation remarkably well.

Case 2. NCBH #139372. B.S., a 19-year-old boy, was first admitted to the North Carolina Baptist Hospital on Oct. 5, 1951. He complained at that time of headaches, nausea, vomiting, and diplopia of 8 weeks' duration. He had difficulty reading fine print, and about 3 weeks prior to admission had noted numbness of the right side of his face.

Examination. His pupils were dilated and reacted poorly to light. There was no ptosis of the eyelids and extraocular movements were normal. The blind spots were enlarged, but there were no visual field defects. There was severe bilateral papilledema. He had a slightly decreased sensibility to pin prick over the right side of his face. Reflexes and coordination were normal. There were no palpable masses in the testes. Genitalia were normally developed.

Roentgenograms of the skull showed midline calcification in the region of the pineal body. On Dec. 7, 1951 the patient underwent ventriculography which demonstrated dilatation of the lateral ventricles and the anterior part of the third ventricle with a rounded mass presenting in the posterior portion (Fig. 3). There was no air seen in the fourth ventricle. Fluid removed from the lateral ventricles at this time contained 10 "mononuclear cells" per c.mm.

Operation. The posterior fossa was explored and the cerebellar tonsils were found to be herniated into the foramen magnum. There was no evidence of tumor in the cerebellum or fourth ventricle, but a catheter passed into the aqueduct of Sylvius met with an obstruction. A ventriculocisternostomy was done.

Postoperative course was uneventful and the patient was discharged from the hospital asymptomatic to receive roentgen therapy on an outpatient basis. He was treated with 200 kV.; 50 cm. target distance; 58 r per min.; 1 mm. Cu filter; through 4 seven-cm. ports, directed toward the posterior third ventricle, receiving 1000 r through each.

2nd Admission, Feb. 3, 1952. The patient had done well since his discharge from the hospital except for occasional dull headache and some vomiting associated with roentgen therapy. He was admitted for re-evaluation and to have ventriculography repeated. On Feb. 4, 1952 a ventricular tap was done and the pressure in the lateral ventricle was about 30 mm. of cerebrospinal fluid. Three to 4 cc. of air were injected

FIG. 3. *Case 2.* Ventriculogram, lateral view. The lateral ventricles are enlarged and there is a mass in the posterior portion of the third ventricle. Note also calcification in region of the pineal body.

before the procedure was discontinued, but subsequent roentgenograms failed to demonstrate the ventricular system. The patient was discharged, his condition essentially unchanged.

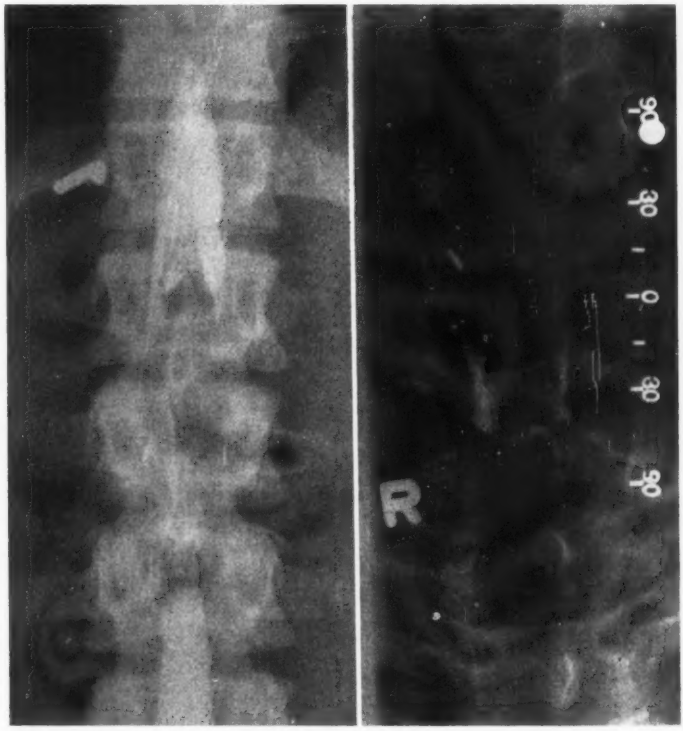
3rd Admission, Oct. 20, 1953. Starting about 4 months prior to this admission, the patient noticed numbness of the backs of his legs. This gradually progressed until several days before admission when he sustained a severe burn of his buttocks while leaning against a steam radiator.

Examination. The area of the posterior fossa decompression was flat. There was anesthesia over the L4 through S5 segments on the left, and hypesthesia over S2 through S5 segments on the right. The left ankle jerk was absent. He had very poor anal sphincter tone.

The spinal fluid contained 1,000 cells per c.mm. (98 per cent mononuclear cells); protein was 298 mg. per cent. A myelogram demonstrated a mass extending from L1 through L3 (Fig. 4).

Operation. An upper lumbar laminectomy was performed, disclosing a pink-grey tumor about 8 cm. in length surrounding the roots of the cauda equina. Some of this was removed and the dura mater was left open.

Course. Following surgery, the patient was on catheter drainage for 2 weeks, after which he was able to void satisfactorily. The sensory loss and reflex changes in



FIGS. 4 and 5. *Case 2.* (*Left*) Lumbar myelogram demonstrating the defect in the radio-opaque column extending from over the body of L1 to the body of L3. (*Right*) Cervical myelogram with the patient in an almost vertical head-down position, showing the spinal block at the C5-C6 level. The silver clip shown is presumed to have come from previous operations either in the posterior fossa or lumbar region.

his legs persisted. He was given a course of roentgen therapy, receiving 2970 r to the lower dorsal and lumbar spinal column.

Following this therapy he returned to college and got along well.

4th Admission, Aug. 10, 1954. Three weeks before this admission the patient began to have aching and stiffness in the muscles of his neck and shoulders, and tingling in his hands. For the last 5 days he had noted increasing weakness in his legs.

Examination. He had hypesthesia up to the C4 level with hyperactive reflexes in his arms and right leg. There was generalized weakness of all muscle groups, especially those of the shoulder girdle and right arm. The bladder was distended to the umbilicus.

Lumbar puncture revealed a complete manometric block. The fluid was xanthochromic with protein of 725 mg. per cent and 107 cells per c.mm. These cells for the most part resembled mononculear cells, but occasional larger cells very similar to the pineal parenchymal cells were seen. A myelogram was done which showed a complete block at the C5–C6 level (Fig. 5). The oil passed freely over the T12-L4 area in which, prior to roentgen therapy, there had been a complete block.

Operation. Cervical laminectomy was done on Aug. 11, 1954. The dura mater was full and bulging at the C4–C5 level and on opening it the leptomeninges were cloudy in several areas. The dentate ligaments were cut, and on moving the cord to the left a grey tumor was found anterior and lateral to the cord on the right. Biopsies

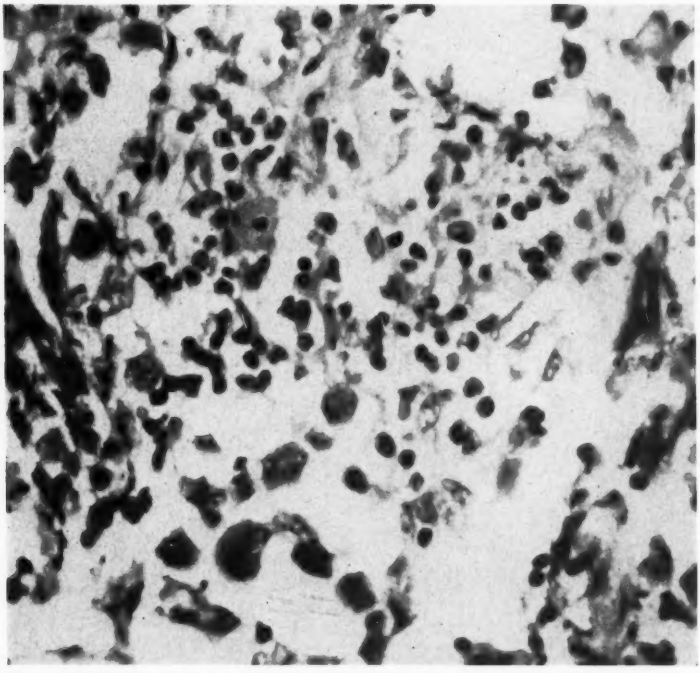


FIG. 6. *Case 2.* Photomicrograph of the tumor taken from region of the cauda equina. Hematoxylin and eosin stain, ×660.

of this were taken as well as a biopsy of the leptomeninges, and the dura mater was left open.

Course. The patient regained strength slowly. He was started on roentgen therapy on his 7th postoperative day, beginning over the cervical region. He was given 2100 r to the cervical spine over a 6-day period, and an additional course through 2 oblique ports of 1800 r each after an interval of 1 month. The complete spinal axis was treated during this series, giving 2400 r to the thoracic spine and 2100 r to the previously treated lumbar area.

He responded well and left the hospital 6 weeks after operation. He was able to use his arms well and was able to walk for moderate distances unassisted.

The patient gradually regained strength in both arms and legs over a 7-month period. About this time he began to notice polydipsia and polyuria and within 3 to 4 weeks he had an intake of approximately 10,000 cc. per day. Because of these symptoms he has been started on another course of radiation to the anterior portion of the third ventricle, and is also being treated symptomatically with pitressin tannate in oil intramuscularly. He has shown no evidence of any further difficulty from his spinal lesions. His shoulder girdle muscles are moderately weak, but the reflexes are normal and his sensory level is no longer present.

Pathology. NCB No. 53-3863. Cauda equina tumor (Fig. 6). There are large cells with vesicular nuclei, some of which show one or two nucleoli. These cells have a

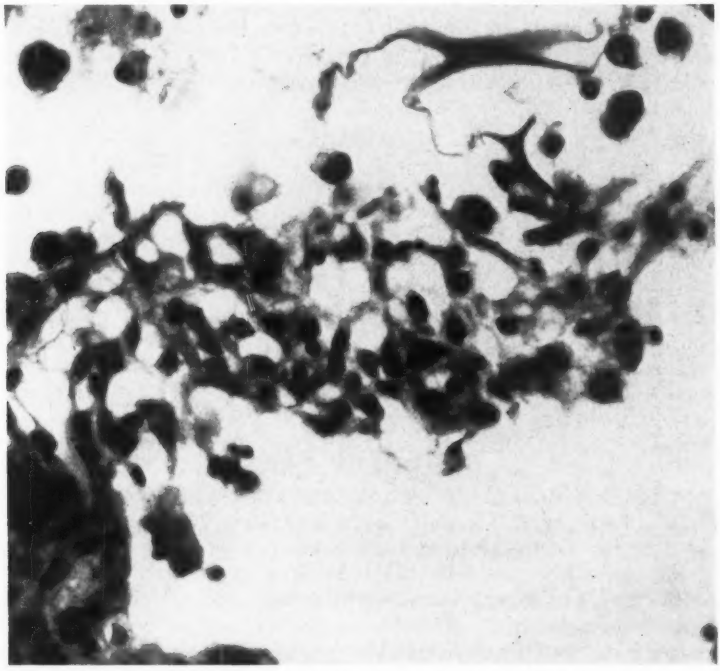


FIG. 7. *Case 2.* Specimen taken from cervical leptomeninges. Note thickening of meninges and diffuse implantation with cells similar to those found in tumor removed at operation. Hematoxylin and eosin stain, ×660.

moderate amount of cytoplasm. There are also smaller cells with hyperchromatic nuclei and scant cytoplasm. Strands of collagenous connective tissue extend about the blood vessels and around the more cellular areas of the neoplasm. Diagnosis: Pinealoma.

NCB No. 54-3161. Biopsy of cervical tumor and cervical leptomeninges. The tumor resembles the original biopsy, but the large cells have more hyperchromatic nuclei and the lymphocytic elements are more abundant. The arachnoid membrane is infiltrated with numerous cells of both large and small types morphologically similar to those in the main tumor (Fig. 7).

Comment. On this patient's first hospital admission a lumbar puncture was not performed because of the presence of increased intracranial pressure. It is interesting to note, however, that the ventricular fluid contained 10 "monocytes." On his 4th admission the cell count in the spinal fluid was elevated, and large cells similar to those seen in the pineal parenchyma as well as the small lymphoid cells were observed on smear. At operation, the biopsy of opaque areas in the cervical leptomeninges showed definite microscopic tumor implants. There is a substantial amount of evidence, therefore, that the medium of spread of the neoplastic cells was the cerebrospinal fluid.

On each occasion when this patient's tumor has been treated locally by roentgen therapy there has been definite clinical evidence of improvement. Further indication of the efficacy of this treatment is given by the fact that the myelographic defect in the upper lumbar region noted in October 1953 had completely resolved by the time myelography was repeated in August 1954.

Case 3. NCBH #181817. B.B., a 20-year-old girl, came to the North Carolina Baptist Hospital on March 4, 1954, complaining of headache, nausea and vomiting, blurred vision and staggering gait. She first noted trouble with her vision 1 year prior to admission, and 6 months later this became associated with generalized headache. As her headaches grew progressively worse she had nausea and vomiting. Her vision became steadily poorer, especially in the left homonymous field. For 2 months she had noticed a numb feeling over the right side of her face and about this time her gait became ataxic with a tendency to stagger to the right. For 5 weeks she had been bedridden because of the severity of these symptoms.

Examination. The patient was a young girl, fairly well nourished, but appearing chronically ill. Visual acuity was poor, and there appeared to be a left homonymous field defect. The fundi showed 4 D. of papilledema bilaterally with hemorrhages on and about the nerve head. The pupils were moderately dilated and did not react well to light or in convergence. Extraocular movements were normal. There was ataxia of the extremities, worse on the right than on the left. The reflexes were equal and active. Sensation was normal over the entire body. There was no evidence of a mass in the nasopharynx.

Laboratory Findings. Urinalysis and blood counts were normal. Serologic examination for syphilis was negative. Roentgenograms of the chest were normal. Skull films showed slight widening of the suture lines and erosion of the posterior clinoid processes. There were some stippled areas of calcification 3.5 cm. posterior to, and slightly above the sella turcica.

Operation. On March 5, 1954, the patient underwent ventriculography. The intraventricular pressure was elevated, and roentgenogram demonstrated a mass in the posterior part of the third ventricle (Fig. 8). After this, a posterior fossa exploration was carried out. In exploring the fourth ventricle fluid was not observed to pass through the aqueduct of Sylvius. The vermis of the cerebellum showed two small pinkish areas of discoloration on its inferior aspect which were removed for pathologic examination. A rubber catheter was placed beneath the scalp, shunting the cerebrospinal fluid from the left ventricle to the cisterna magna.

Course. The patient did well following surgery except for slight persistent nausea.

She was discharged on her 10th postoperative day and was referred to a radiologist near her home for therapy. She was given 3,000 r (in air) through each of 3 ports to the region of the posterior third ventricle and 2,500 r (in air) to each area of the spinal column.

2nd Admission, March 29, 1955. The patient was getting along well except for occasional nausea which was well controlled with medication until 3 weeks prior to readmission, when she began to notice numbness over the right side of her face and body. She also had occasional spells of weakness of the right arm and leg.

Examination. She had horizontal nystagmus on right lateral gaze and weakness of the left lateral rectus muscle. There was hypalgesia over the right side of the face with right peripheral facial weakness. There was hypalgesia over the right side of

FIG. 8. *Case 3.* Ventriculogram, brow-down position. Note mass with stippled calcification in posterior portion of third ventricle.

the body which faded out at about the T2 level. Deep tendon reflexes were increased in the right arm and leg. Roentgenograms of the skull showed a marked increase in the calcification in the region of the pineal and midbrain.

A myelogram was done to check on the possibility of a cervical metastasis as a cause for the peripheral neurologic findings. This was normal to the upper cervical region. It was therefore concluded that the patient probably had extension of her tumor locally into the thalamic region and possibly into the posterior fossa. She was then discharged to receive further roentgen therapy to these regions.

3rd Admission, May 3, 1955. The patient returned to the Outpatient Department on the day of admission for a follow-up visit after 11 roentgen treatments. She was feeling better except for slight headache and occasional "weak spells." She had not noted much change in the numbness of her extremities, but her facial weakness was definitely improved. Before leaving for home she said she had a headache and felt quite faint, and because of this she was readmitted to the hospital.

Examination. She showed moderate right facial weakness as well as some loss of hearing in the right ear. There was no evidence of papilledema. She still had a left

lateral rectus weakness. There were ataxia and weakness of the right hand. Deep tendon reflexes were increased on the right. There was still a suggestion of a sensory level in the upper thoracic region on the right, but this was not as well demarcated as on the previous examination.

Course. The patient was given a high protein diet and bed rest for several days. During this time she appeared to be much improved and she was discharged to continue her roentgen treatment. Further roentgen therapy was given to the posterior fossa during June 1955, but because of the patient's continued downhill course

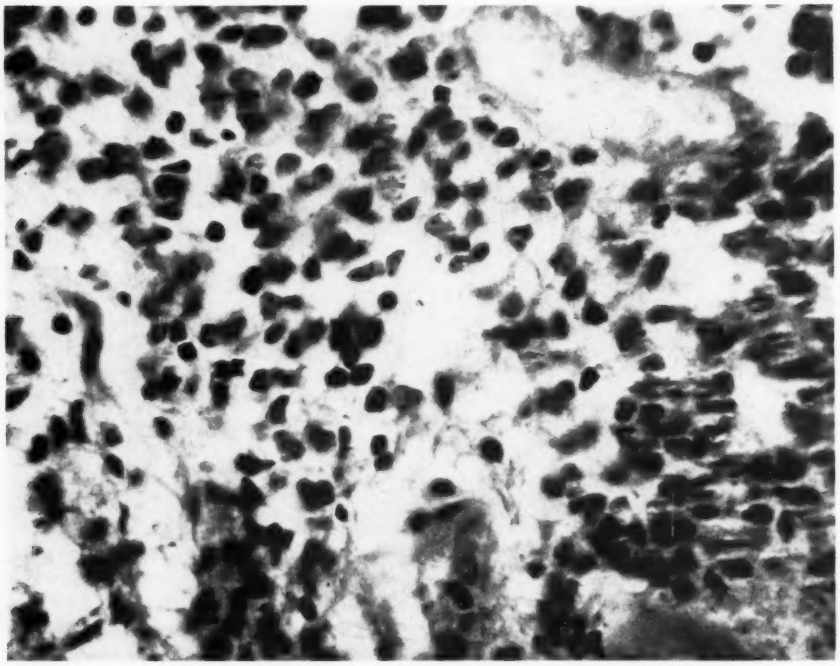


FIG. 9. *Case 3.* Photomicrograph of cerebellar biopsy. Hematoxylin and eosin stain, ×570.

and the difficulties associated with her being taken to the radiotherapist, this could not be consistently followed. A right facial weakness of peripheral type developed, associated with subjective hypalgesia of the right side of the face. It was considered clinically that she showed evidence of a progressive lesion in the right cerebellopontine angle.

She died at home on Aug. 12, 1955. An autopsy was performed by Dr. S. S. Hindman of Waynesville, N.C. The brain was removed and delivered to Dr. Martin Netsky. The spinal cord was not removed. The general postmortem examination showed no evidence of primary or metastatic tumor.

Dr. Netsky reviewed the original specimen of tumor taken from the cerebellum at operation and concurred in the diagnosis of pinealoma. On examining the brain he remarked that there was very little neoplasm remaining in the specimen. A small

portion of this was seen just behind the collicular plate, where it extended as a finger-like projection into the leptomeninges. There were extensive areas of destruction of the cerebellum and brain stem, presumably secondary to the radiation therapy.

Pathology. NCB No. 54-893. Biopsy of a nodule from the surface of the cerebellum (Fig. 9). There are masses of large cells showing some variation in size. The nuclei of these cells are vesicular and nucleoli are present. There are some areas of smaller, hyperchromatic cells which are not intermingled with the large cells. Special stains showed no evidence of reticulin being laid down by the tumor. Diagnosis: Pinealoma.

Comment. Admittedly the histologic picture of the tumor could have suggested other types of neoplasm such as nasopharyngeal lymphepithelioma or dysgerminoma. There was neither clinical nor postmortem evidence of primary tumor elsewhere. The increasing calcification in the pineal region in more recent roentgenograms gives further positive evidence of the nature of this tumor.[8] It is unfortunate that the postmortem examination performed elsewhere did not include the spinal cord. The very striking changes in the cerebellum, apparently secondary to roentgen therapy administered at our request, and the small residual tumor present in the pineal region bear adequate evidence both to the effectiveness of such therapy to this pinealoma and to the possible destructive effects on normal nervous tissue. Since there was no evidence of increased intracranial pressure clinically before her death or at postmortem examination, it is possible that the effect of roentgen radiation on the brain stem and midbrain may have contributed to her terminal course.

DISCUSSION

From the cases reported in the literature was well as the 3 cases summarized in this paper, it has been shown that tumors of the pineal body have a definite ability to metastasize within, and occasionally outside of the central nervous system. It has not been determined whether certain types of tumor have a greater propensity in this regard than others. This is attributable in part to the variations encountered in the pathologic classification of these lesions, and in part to the fact that many of them are treated by irradiation without a pathologic specimen being obtained.

Pathologically, tumors arising in the pineal region show much variation in their histologic structure. Some observers[15] feel that in spite of this, these lesions fall into one neoplastic group, reflecting in their cellular constituents some stage in the embryologic development of the pineal body. Russell,[29] however, believes that although neoplastic transformation of pineal cells may rarely occur, the majority of tumors arising in this region are actually teratomas or teratoid growths. She stated that there are morphologic differences between the normal pineal cells and those of the pineal tumors. She also found that serial sections of most "pinealomas" show cellular elements that would more properly classify them as teratomas, and that most teratomas arising in the pineal region have areas showing typical pineal structure. Walton[37] gave further support to this theory in his report of a case of a

typical teratoma of the pineal body which seeded into the hypothalamic region and in this location took the form of a teratoid growth with pinealomatous areas. Occasionally these lesions are immature enough to warrant classifying them as chorionepitheliomas.[32] McGovern[22] has grouped pineal tumors under five headings: pinealoblastoma, pinealocytoma, ganglioneuroma, glioma, and teratoma (which he considers to be the most common tumor of the pineal region). Several cases have also been reported of diffuse involvement of the ependymal surface without the presence of a primary tumor in the region of the pineal body.[13,23,28] Russell explained this by stating that because most pineal body tumors are teratomas they may closely resemble teratomas arising from other sites within the brain. It is the feeling of some,[20,24] however, that true ectopic pinealomas may occur. Despite the variance in these opinions it is known that teratomas, chorionepitheliomas, pinealoblastomas, and pinealocytomas may metastasize by means of the cerebrospinal fluid. These represent the majority of tumors arising in the region of the pineal body.

Attempts at surgical extirpation have been carried out in the past but, in general, the results of such operations have been quite disappointing.[10,25] Because of the high mortality associated with direct surgical attack, the more generally accepted method of management at present is to relieve the increased intracranial pressure by ventriculocisternostomy,[35] subtemporal decompression,[18] or third ventriculostomy,[31] followed by roentgen therapy to the posterior portion of the third ventricle. When these methods of treatment are used, the exact histology of the neoplasm usually is not known. This is in opposition to the well-founded rule of not giving radiation to a lesion of undetermined pathology, but even biopsy of a tumor in this region may have fatal consequences, and from the patient's standpoint a more conservative, albeit blind, approach is frequently more satisfactory.

The potent effect of radiation on these tumors is well exemplified by our Cases 2 and 3, as well as Case 2 of Tompkins *et al.*[34] in which a tumor incompletely removed at surgery was irradiated postoperatively and at postmortem examination was found to have been completely destroyed. Horrax[17] reported a series of 22 pineal tumors, 14 of which had been verified by operation or autopsy. The other 8 were diagnosed on the basis of neurologic and ventriculographic findings. Of 10 patients who had gross operative removal, 3 were living 10, 5 and 3 years after operation. These 3 patients had also been given postoperative irradiation to the pineal body (a fact that may have some bearing on their survival). Of the 12 patients who received only decompression or biopsy and radiation therapy, 7 were alive 2 to 15 years later, and one other patient was living 3 months after therapy. Four of these conservatively treated patients died within a few days to 1 year following operation. Horrax feels on the basis of his experience with these tumors that the results obtained with decompression and irradiation are superior to those with radical surgery.

Because a variety of tumors of the pineal region may spread *via* the cerebrospinal fluid pathways, it suggested that even though a definite micro-

scopic diagnosis can rarely be made prior to treatment, total irradiation of the central nervous system might be advisable in those patients showing a mass lesion in the posterior third ventricle. This would seem to be a more rational approach than awaiting the clinical appearance of metastases (as in Case 2) and then treating each of these recurrences individually. It is entirely possible that cells may shed from an untreated and clinically undetected metastasis, and thus diffuse spread of the tumor will occur back into areas previously treated by X-ray.

Various methods have been suggested for the complete irradiation of the central nervous system. The most generally used is the multiple port technique. More recently, the use of a single spade-shaped field covering the entire cerebrospinal axis has been suggested for the treatment of medulloblastomas.[26] This could be used in conjunction with supplementary ports to the head to very good advantage in the therapy of pineal tumors. Work has also been done on the use of intrathecal radioactive colloidal gold,[12] but this has not been investigated sufficiently to justify its clinical use at present. From the cases tabulated in Table 1 it would seem especially important to

TABLE 1

Previously reported pineal tumors with metastases

Author	Year	Site of Metastasis	Pathology
Horrax and Bailey[19]	1925		
Case 2		Meninges over surface of cerebellum, and about brain stem	Spongioblastoma
Case 4		Floor of 3rd ventricle	Pinealoma
Berblinger[6]	1925	Cauda equina	Pinealoma
Fulton and Bailey[14]	1929		
Case 5		Hypophysial stalk and optic nerves	Pinealoma
Cairns and Russell[7]	1931		
Case 1		Spinal metastases	Unclassified glioma
Alajouanine *et al.*[2]	1934	Third ventricle and implants along cord with areas of intramedullary invasion	Neurospongioma (medulloblastoma) originating in pineal region
Stringer[33]	1934	Tuber cinereum	Pinealoma
Friedman and Plaut[13]	1935	Cauda equina and diffuse spread over cranial nerve roots	Pinealocytoma (a primary tumor was not found in region of epiphysis)
Alajouanine *et al.*[1]	1937	Posterior 3rd ventricle and 4th ventricle; seeding over surface of 3rd and lateral ventricles, olfactory bulb; spinal cord and nerve roots diffusely involved	Pinealoma
Van Gehuchten and Callewaert[36]	1937	Third and lateral ventricles	Pinealoma

TABLE 1—*Continued*

Author	Year	Site of Metastasis	Pathology
Baggenstoss and Love[3]	1939	Suprachiasmatic region and lumbar spinal canal	Pinealoma
Mackay[23]	1939	Diffuse ependymal involvement	Pinealoma
Werner[38]	1939	Diffuse meningeal and ependymal involvement	Pinealoma
Russell and Sachs[30]	1943	Seven out of 18 cases showed spread into subarachnoid spaces or ventricles	Pinealoma
Dublin[11]	1945	Microscopic dissemination over surfaces of cerebrum, cerebellum, and spinal cord	Pineal ependymoma
Stowell *et al.*[32]	1945	Third ventricle and lung	Chorionepithelioma
Horrax and Wyatt[20]	1947		
Case 1		Microscopic invasion of posterior lobe of pituitary and ependyma	Pinealoma
Case 2		Suprachiasmatic region	Pinealoma
Case 3		Suprachiasmatic region	Pinealoma
McGovern[22]	1949		
Case 2		Third ventricle	Pinealoblastoma
Case 4		Third ventricle	Pinealoblastoma
Walton[37]	1949	Hypothalamic region	Primary: teratoma; metastasis: atypical teratoma with pinealomatous regions
Baker and Rucker[5]	1950	Optic chiasm (found at operation); spinal cord (progressive paraplegia developed later, presumably caused by same tumor). No autopsy reported	Pinealoma
Tompkins *et al.*[34]	1950		
Case 1		Centrum ovale, straight sinus, and lung	Teratocarcinoma
Case 2		Spastic paraplegia developed 6 months before death. Lung and tracheobronchial lymph nodes (spinal cord not examined at autopsy)	Pinealoma
Rand and Lemmen[27]	1953		
Case 2		Region of optic chiasm	Pinealoma
Case 3		Optic nerves and septum pellucidum	Ectopic pinealoma (pineal body normal histologically)
3 cases		Spinal cord involvement indicated by radicular symptoms and signs	Posterior 3rd ventricle tumor shown by ventriculogram
Ray[28]	1953	Ependymal lining of ventricles, right internal capsule, posterior pituitary and infundibular stalk	Pinealoma (pineal body not present at autopsy)

give adequate treatment to the region of the third ventricle, the suprachiasmatic structures, and the cauda equina as these appear to be the most frequent sites of metastasis.

SUMMARY

Three cases have been presented illustrating the potentiality of tumors originating in the pineal region to metastasize *via* the cerebrospinal fluid. Literature pertaining to the spread of pineal tumors by various routes has been reviewed, and the implications relating to the therapy of these neoplasms have been outlined. It is suggested that these tumors be treated by operative decompression followed by irradiation of the complete cerebrospinal axis.

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THE POSTERIOR-PERITONEAL SHUNT TECHNIQUE FOR THE TREATMENT OF INTERNAL HYDROCEPHALUS IN INFANTS

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INCREASING reports of promising results following shunt operations in the treatment of hydrocephalus make worth while the report of a technique that has been used on our service during the last 4 years with relatively good results. The frequent complications that follow the usual subarachnoidal-peritoneal shunt by placing the catheter in the right lower quadrant led us to try different procedures, and finally to place the catheter in the retro-omental space.

TECHNIQUE

Under local anesthesia or, better, intratracheal ether, the patients are placed face down on the operating table and the legs are elevated until the lumbar spine is above the level of the head. Children should be firmly fastened to the table (Fig. 1A).

A vertical incision is made centering in the spine of L3, and extending to L4 and L2 (4 cm. long in babies and longer in adults). After reflecting the spinal muscles, laminectomy of L3 is carried out (Fig. 1C).

Two parallel threads are placed in the dura mater, including the arachnoid membrane on it. In order to catch the arachnoid in the stitch, an assistant presses on the fontanel or raises the head of the patient for a moment, and the increased cerebrospinal fluid pressure in the lumbar sac will bring the arachnoid against the dura mater. Incision of the dura mater and arachnoid is made exactly between and parallel to the threads and not longer than 0.5 cm. A polyethylene tube (not smaller than 0.3 cm. diameter) is placed caudally in the subarachnoid space at a depth of approximately 3 cm. A lateral hole may be placed in the tube about 1 cm. from its end. The threads are tied tightly around the tube (Fig. 2B).

A second incision about 5 cm. long is carried out just above the last rib and following its direction, starting halfway above the spinal muscles. If the last rib is long, a fragment of it should be removed (usually no more than 3 cm.) in order to facilitate exposure, otherwise the incision of muscle and fascia follows the lower edge of the rib. After exposing the renal fat, further dissection is carried out directing attention mesially rather than laterally in the cavity. With wet gauze and retractors the renal fat is pushed down and detached from the diaphragm until the liver is exposed. Usually, under the lower face of the liver the peritoneum is visualized. It can be picked up with a forceps, and opened for a distance of no more than 2 cm. (Fig. 2A, C).

At this point, with a long pointed forceps, a track is made through the spinal musculature and the catheter is brought through it into the abdominal cavity, taking care to avoid acute angles by sectioning tendinous and muscular insertions until a smooth curve is obtained. Some air bubbles are permitted to remain in the

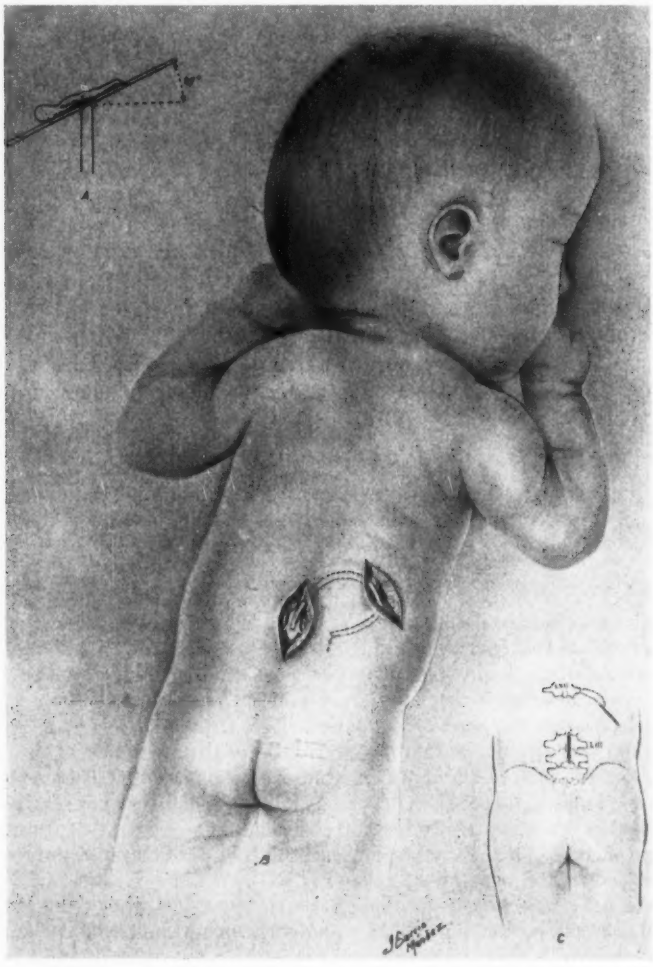

FIG. 1. (A) Position of patient for surgery. (B) Final placement of the catheter. (C) Incisions.

catheter in order to repeatedly reaffirm the permeability of the catheter by raising and lowering the patient and observing the motion of the air bubbles.

The peritoneal end of the catheter is placed into the peritoneal opening under the liver, being careful to direct the catheter mesially and not in a lateral direction. A purse-string closure is made around the catheter and again the flow of cerebrospinal fluid is checked by watching the air bubbles move when the pressure of the

cerebrospinal fluid is increased. Closure in layers is then carried out (Fig. 1B).

The patient is kept in the head- and face-down position for 1 week after surgery. Then, gradually the patient is turned up and the mother is instructed about the

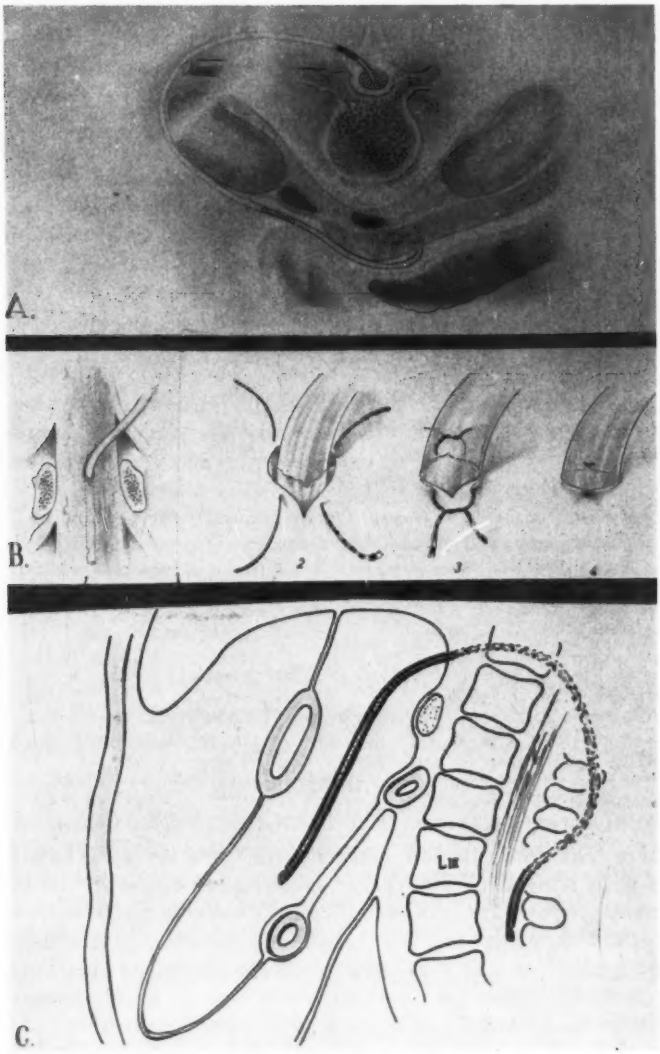

FIG. 2. Anatomical diagrams of (A) transverse and (C) sagittal views of the catheter in place. (B) Detail of the dural stitch.

possibilities of hypotension (vomiting, headache, sunken fontanel), and the way to treat it by bringing the head down. We have not seen symptoms of severe hypotension lasting more than a month after surgery.

COMMENTS

In Table 1 we have compared our experiences with peritoneal shunts in infants. With the anterior-peritoneal technique our main difficulties have been:

(A) *Obstruction of the tube* by
- 1. The omentum ..... 3 cases
- 2. A fibrinous plug ..... 1 case
- 3. Kinking of the tube ..... 1 case

(B) *Cerebrospinal fluid fistula* caused by
- 1. Infection ..... 3 cases
- 2. A defect in wound closure ..... 3 cases
- 3. Slipping of the tube ..... 1 case

(C) *Others*
- 1. Sudden death ..... 3 cases
- 2. Convulsions ..... 1 case
- 3. Paralysis of arms ..... 1 case

The great majority of the difficulties with obstruction of the tube and formation of a cerebrospinal fluid fistula may be overcome by improvement

TABLE 1

*Effects of peritoneal shunts for treatment of communicating hydrocephalus in infants**

Anterior-Peritoneal Shunt			*Posterior-Peritoneal Shunt*		
Arrested		11 cases	Arrested		9 cases
Complications	5		Complications	2	
Reoperations	3		Reoperations	2	
Not arrested		12 cases	Not arrested		1 case
Reoperations	2		Reoperations	0	
Operative deaths	5		Operative deaths	0	
Total		23 cases	Total		10 cases

* Follow-up period 12 to 50 months.

in operative technique. In fact, most fistulas were recorded in our first experiences with peritoneal shunts and none has occurred in the last 23 patients operated upon. The 3 infected patients suffered from spina bifida and without doubt they were already contaminated when plastic repair of the defect and peritoneal shunt procedure were attempted in one stage.

Sudden death within the first 24 hours was an early experience with these procedures. In 2 of the patients no abnormality was found at necropsy. These fatalities, as well as the complication of early postoperative convulsions, were presumed to be related to postoperative cranial hypotension and have led us to keep the patient's head down for many days following surgery. In 1 patient affected with severe spina bifida in whom a peritoneal shunt had been carried out 2 years previously, symptoms of progressive flaccid brachial palsy developed bilaterally. The hydrocephalus was under con-

trol, and the paralysis was thought to be related to an Arnold-Chiari malformation. Unfortunately, the patient never returned for further recheck examinations.

One of the most difficult complications to overcome has been plugging of the tube by the omentum or by fibrinous adhesions. Largely, the same difficulties led Scott *et al.*[2] to carry out 67 operations in 32 infants. Spitz and Koop[3] improved their results by removing the omentum and using a lucite peritoneal button. Jackson[1] with a rather long experience lately has been placing the tube above the liver trying to overcome the same difficulties.

We have 10 cases in which operation was performed by the posterior-peritoneal technique. The patients have been followed from 12 to 50 months postoperatively. Nine have shown a definite arrest in their hydrocephalus and the only failure was a patient who died because of diarrhea and a lumbar cerebrospinal fluid fistula. Only 2 patients required reoperation: one 7 days after surgery, because the lateral hole of the catheter slipped out of the dura mater, and the other 11 months after surgery because of fibrinous plugging of the peritoneal end. There has been no difficulty with the omentum thus far.

The advantages of the above-described procedure appear to be: (i) The entire procedure is performed in the face-down position. (ii) The shorter distance between spine and peritoneum. (iii) Avoidance of the omentum. (iv) Protection of the tube within the muscle.

The postero-anterior placement of the tube in the shape of a curve with lower concavity, makes less likely the possibility of displacement by the growth of the child. The growth in thickness is considerably less than it is in height.

It is difficult to state if actually we have been placing the catheter into the retro-omental space (behind the stomach) in all cases. However, the results with the posterior-peritoneal technique in this short period of observation appear to warrant further trials and developments.

SUMMARY

A technique for posterior-peritoneal (retro-omental?) shunt for the treatment of communicating internal hydrocephalus is described.

Of 10 patients in whom this procedure was tried, 9 showed arrest of hydrocephalus during 12 to 50 months, and only 2 needed revision.

Comparative data are given for the anterior-peritoneal shunt.

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CASE REPORTS AND TECHNICAL NOTES

SUCCESSFUL TREATMENT OF AN ANEURYSM OF THE ANTERIOR COMMUNICATING ARTERY

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Among the various types of intracranial aneurysms, saccular aneurysms of the anterior communicating artery deserve special consideration. Because of their location at a crucial point of the circle of Willis, rupture is particularly dangerous and treatment is hazardous. A review of the literature reveals that relatively few instances of aneurysms in this location have been successfully treated. By "successful" I mean that not only is good recovery obtained after one or several subarachnoid hemorrhages have occurred but subsequent bleeding is avoided. This can be accomplished with certainty only by the complete isolation of the aneurysmal sac from the blood stream. Two procedures assure this goal: one is to occlude with clips or tie the neck of the aneurysm with a silk ligature, and the other is "trapping" of the aneurysm. For aneurysms of the anterior communicating artery, the procedure of "trapping" seems very difficult, as pointed out by Poppen[11] among others, because the artery is extremely short. Ligature of the neck of the aneurysm undoubtedly is the ideal method, as Norlén[8,9] has recently stressed. His reports indicate that the neck can be clipped in quite a number of cases, disproving previous ideas that this procedure is almost impossible.

In a survey of the pertinent literature, 39 cases of aneurysm of the anterior communicating artery treated by the intracranial approach were found in which detailed description was given of the procedure performed.[1–7,10,13] In 4 of the 39 cases the operation was limited to exploration of the lesion or evacuation of an intracerebral hematoma; the aneurysm itself was not treated.[6,10] I have not included in the 39 cases 8 patients in whom both anterior cerebral arteries were occluded; 5 of the 8 died and the condition of 2 who recovered remained severely impaired.[4,6] These cases were excluded because the extensive procedure unquestionably was performed under unexpected circumstances as a life-saving measure. Thirty-five of the 39 patients were treated by all the known methods but in only 23 cases was a definitive procedure accomplished. Eighteen of these 23 cases were reported by Norlén: in 17 the neck of the aneurysm was ligated with 1 casualty, and in 1 "trapping" was performed, resulting in death. Of the remaining 5 patients, 2 died (2 of these patients had ligatures of the neck of the aneurysm, 2 ligatures of the neck combined with clipping of one anterior cerebral artery and 1 "trapping"[1,3,6]).

Steelman *et al.*[12] did not report any case of aneurysm of the anterior communicating artery in their series of 42 lesions operated upon intracranially. Poppen[11] stated that in not a single case of aneurysm in this location was the neck of the aneurysm suitable for insertion of a clip.

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It has recently been emphasized that a more detailed description must be given in all cases of intracranial aneurysms reported; various factors (location, time of operation, existence of hematoma, and so forth) that may influence the final outcome should be included. For this reason it seems worth while to report a single case of aneurysm of the anterior communicating artery successfully treated by direct intracranial attack. It is our only experience with the intracranial approach for saccular aneurysms.

CASE REPORT

A 34-year-old man was admitted to the hospital on April 18, 1955. He had had short episodes of unconsciousness, presumably convulsions, since the age of 18 years. Three weeks before admission, the patient felt dizzy, fell, and was unconscious for about half an hour.

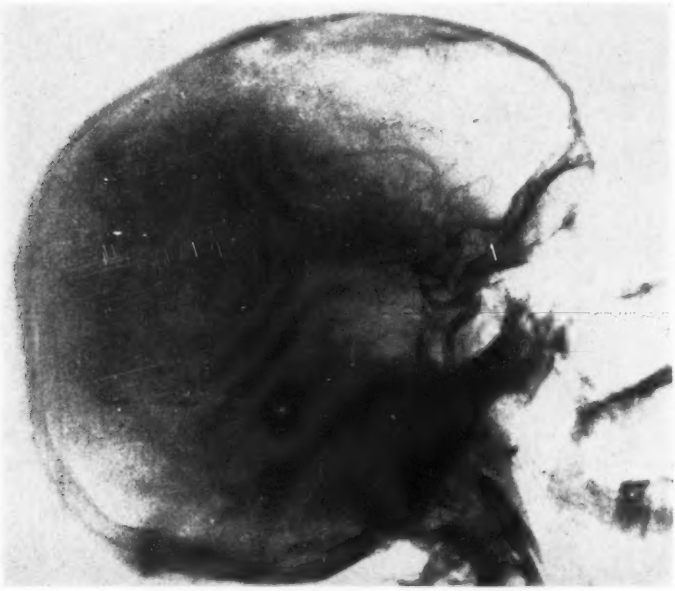

FIG. 1. Right carotid arteriogram. The aneurysm is visible arising from the anterior communicating artery.

The episode occurred just after defecation. He had had severe headaches and vomiting for a few days and then had begun to improve. About a week later he was able to get up and walk around, although mild headaches still remained. The day before admission, a similar episode took place. He was unconscious for about 30 minutes; when he regained consciousness he had a severe headache and vomiting occurred.

Examination. The patient appeared to be acutely ill. He was drowsy and complained of constant headaches. The only neurological abnormalities were nuchal rigidity, and a positive Oppenheim's sign on the left. The blood pressure was 120 mm. systolic and 60 mm. diastolic. The pulse rate was 56 and temperature 37.2°C. A lumbar puncture revealed bloody cerebrospinal fluid.

Course. Arteriograms of both carotid arteries were made the following morning while the patient was under Pentothal anesthesia. A small saccular aneurysm arising from the anterior communicating artery was visualized in both the lateral (Fig. 1) and the anteroposterior ex-

posures of the right carotid artery. Both anterior cerebral arteries were filled from the right. After injecting the left carotid artery the aneurysm was not visualized in the lateral and anteroposterior views. The patient tolerated the procedure well.

The following morning the headaches grew worse, the pulse rate increased, there was a rise in temperature to 39°C. and subsequently the patient became unconscious for about an hour. His head was turned to the left and there was a conjugate deviation of the gaze to the same side. A lumbar puncture revealed an increase in blood in the cerebrospinal fluid.

The patient recovered slowly but headaches and drowsiness persisted. The nuchal rigidity and the positive Oppenheim's sign on the left continued to be the outstanding neurological findings.

1st Operation. On April 24, 1955, a right frontal flap was turned down under endotracheal ether anesthesia. The intracranial pressure was reduced by continuous spinal drainage. The

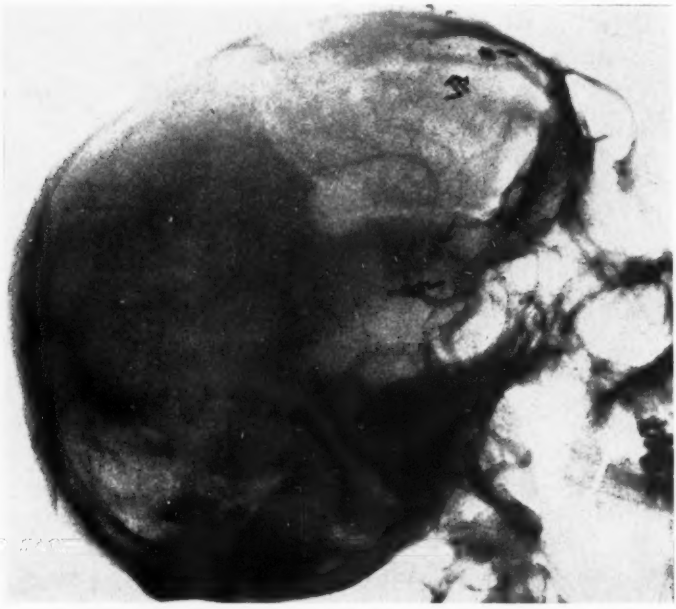

FIG. 2. Left carotid arteriogram after the first operation. The aneurysm is now visible after injecting this side. It appears even larger than before.

bone flap was elevated and the dura mater was opened. The right frontal lobe was retracted along the lesser sphenoidal wing, exposing the optic nerves, the right carotid artery and its branches. A small area of yellowish discoloration was observed in the most posterior portion of the right gyrus rectus on the undersurface of the frontal lobe. We believed that the aneurysm was located there and that the discoloration was caused by previous bleeding. No attempt was made to discover the aneurysmal sac, which was encased in the interhemispherical fissure. Two silver clips were placed on the most medial part of the first portion of the right anterior cerebral artery, just before it enters the interhemispherical fissure.

Course. Recovery was uneventful. The headache disappeared gradually and the nuchal rigidity was gone about a week after the operation. As the general condition of the patient improved, it became apparent that some mental symptoms were present, principally indifference and loss of memory for recent events. These symptoms gradually disappeared.

Twenty-four days after the operation when the patient was practically free from symptoms, arteriography was repeated in order to determine the effect of the ligature of the right anterior cerebral artery upon the aneurysm. On the right side, only the anteroposterior view was taken which showed the obliteration of the right anterior cerebral artery about 1 cm. from its origin from the carotid artery. The aneurysm was perfectly visualized, however, in both the lateral (Fig. 2) and the anteroposterior views of the left carotid arteriogram. The sac seemed to have increased in size since the previous arteriograms. Both anterior cerebral arteries (distal to the anterior communicating artery) could be seen in the anteroposterior exposure of the left carotid arteriogram.

It was decided to attempt a more radical procedure when the patient had recovered fully from the first operation.

2nd Operation. On June 7, 1955, under endotracheal ether anesthesia, the old right frontal flap was re-elevated, and again continuous spinal drainage was used to reduce intracranial pressure. The frontal lobe was displaced upward and the right anterior cerebral artery and the silver clips previously inserted on it were identified. Resection of the most posterior portion of the right gyrus rectus was sufficient to uncover the aneurysm, which appeared as a spherical mass about 1 cm. in diameter, surrounded by dense fibrous tissue. It was located between the frontal lobes in front of the right anterior cerebral artery. Freeing the sac of the aneurysm, the right anterior cerebral artery and the right side of the anterior communicating artery was a time-consuming procedure. The juncture of the aneurysm and the anterior communicating artery was obscured by the right anterior cerebral artery and could not be adequately exposed. We decided to section this artery between clips immediately distal to the anterior communicating artery, thus exposing the origin of the aneurysm from the anterior communicating artery. There was only a slight narrowing between the aneurysm and the artery, across which a silver clip was placed. The aneurysm and adjacent arteries were wrapped with hammered muscle.

While isolating the aneurysm, hypotension was maintained with the use of Pendiomid. The blood pressure was high during the first part of the operation but did not fall below 100 mm. systolic during the remainder of the procedure.

Course. The patient made a rapid recovery and was out of bed 8 days after the operation. There were no obvious mental or neurological symptoms except for the persistent positive Oppenheim's sign on the left.

Left carotid arteriography was repeated 13 days after the second operation. The aneurysm was no longer visualized in the lateral and anteroposterior views. The left anterior cerebral artery was visible in the latter view but the right anterior cerebral artery was not filled with contrast medium.

The patient was last seen 1 month after ligation of the aneurysm. He felt well although he had some neurological abnormalities.

COMMENT

It was shown in this patient that ligation of the proximal portion of the right anterior cerebral artery, which apparently supplied the aneurysm, had no visible effect. On the contrary, the aneurysm was larger after the procedure, and was supplied with blood from the contralateral anterior cerebral artery. It was necessary to section the right anterior cerebral artery to obtain adequate exposure of the neck of the aneurysm and thus avoid inclusion of the left cerebral artery in the ligature. The postoperative course has not revealed any serious sequelae, which might have been expected after closure of this artery, according to the experience of others.

We believe that postoperative arteriograms are of the utmost importance in the evaluation of the direct treatment of saccular aneurysms.

It must be remembered that the first operation in this case was performed during the so-called "acute period" of bleeding intracranial aneurysm and was well tolerated by the patient.

SUMMARY

A case is reported of a saccular aneurysm of the anterior communicating artery. The rarity of reported cases of this condition successfullly treated by direct attack is stressed, except for the published series of Norlén and Olivecrona. Ligation of the anterior cerebral artery proximal to the anterior communicating artery proved to be inadequate, as shown by arteriograms made after the first operation. Subsequent "clipping" of the neck of the aneurysm resulted in a successful recovery.

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GLOSSOPHARYNGEAL NEURALGIA

CAUSED BY COMPRESSION OF THE NERVE BY AN ATHEROMATOUS VERTEBRAL ARTERY

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Apart from reports relating to intra- and extracranial tumours, few observations have been published on glossopharyngeal neuralgia in which a precise cause of this disorder was discovered. Pope[8] reported a case of neuralgia caused by pressure on the glossopharyngeal nerve by a thrombosed vertebral artery, and Lillie and Craig[6] published another in which the cause was an anomalous artery in the cerebello-pontile angle. Ferey *et al.*[4] and Deparis[3] described cases of glossopharyngeal neuralgia caused by arachnoiditis and perineural fibrositis.

In the case presented here, partial degeneration of the glossopharyngeal nerve resulted from compression by an atheromatous vertebral artery.

CLINICAL NOTES

Van A. J., a woman of 77, had had recurrent attacks of angina pectoris since the age of 65. She was first admitted to hospital in February, 1953, suffering from a blood dyscrasia caused by nutritional deficiency. She was readmitted on May 24, 1953, complaining of a neuralgic syndrome which had commenced suddenly 5 days previously.

She had paroxysms of excruciating stabbing pain of short duration brought on by swallowing and movements of the tongue. The pain radiated from the left tonsillar fossa to the left ear and prevented her from eating and swallowing. Short intervals of relief occurred between the attacks of pain. Cocainization of the tonsillar region produced rapid though transient relief.

Examination. The patient showed a generalized severe degree of atheroma. The blood pressure was 160/90 mm. Hg. Otolaryngological and neurological findings were negative. Wassermann's reaction was negative. The blood urea was 26 mg. per cent. The blood platelets were decreased in number: 129,000 per c.mm. on the first occasion, 48,000 per c.mm. on the second occasion. The bleeding and coagulation times were normal. The prothrombin time was 65 per cent of normal. The cerebrospinal fluid contained 3 cells per c.mm.; total protein was 22 mg. per cent. The patient died suddenly on June 9, 1954.

Postmortem examination disclosed myocardial infarction, purulent bronchiolitis, bilateral hydronephrosis and a dissecting aneurysm of the abdominal aorta. A small focus of softening was present in the left putamen. No other macroscopical lesion was found in the brain.

The cerebral arteries showed a severe degree of atheroma and even the smallest parenchymatous vessels were affected. The left vertebral artery ran on the lateral surfaces of the cervical spinal cord and medulla oblongata, then turned towards the basilar sulcus of the pons and alone formed the basilar artery. Below this transverse groove the artery gave rise to the left posterior inferior cerebellar artery. The right vertebral artery, after running its normal course, curved backwards and outwards at the level of the transverse groove separating medulla oblongata and pons and terminated in the right posterior inferior cerebellar artery (Figs. 1 and 2). The origin of the vertebral arteries in the neck was not investigated. At the level of the lower part of the medulla oblongata, the diameter of the right vertebral

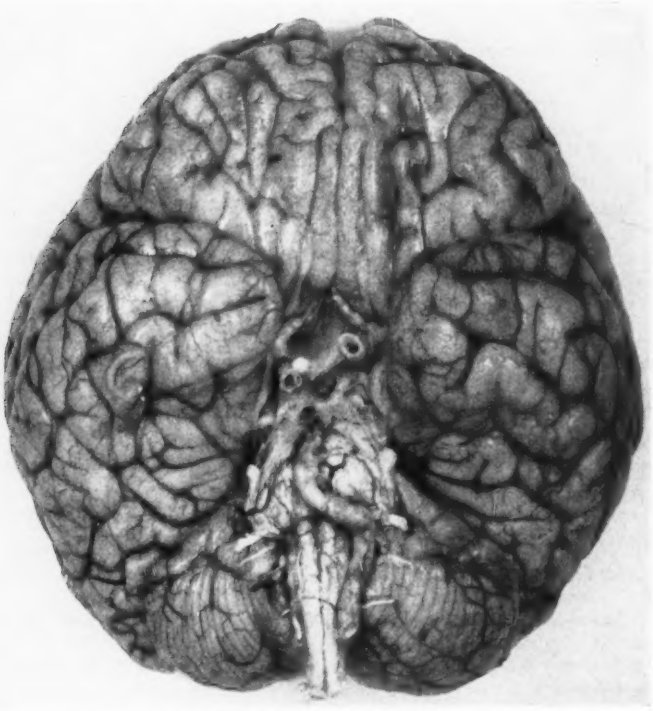

FIG. 1. Inferior aspect of the brain. The vertebral arteries are not united: the basilar artery is formed by the left vertebral artery only.

FIG. 2. The dissected circle of Willis demonstrates nonunion of the vertebral arteries.

artery was 2 mm. and the diameter of the left vertebral artery was 6 mm. The circle of Willis showed inequality in the calibre of the two posterior communicating arteries.

At the level of the transverse groove, the enlarged, atheromatous, left vertebral artery made a depression on the lateral surfaces of the medulla oblongata and pons and on the undersurface of the cerebellum (Fig. 3). In the bottom of this depression, the roots of the nerves IX, X, and XI and the posterior inferior cerebellar artery were compressed. The trigeminal nerves were normal.

The roots of the right and left cranial nerves IX, X, XI, and XII were embedded in paraffin after mordanting in fluorochrome. The cranial nerves IX and X were embedded together. The nerves were cut transversely and stained by the Weigert-Pal method: some sections were counterstained by van Gieson's method.

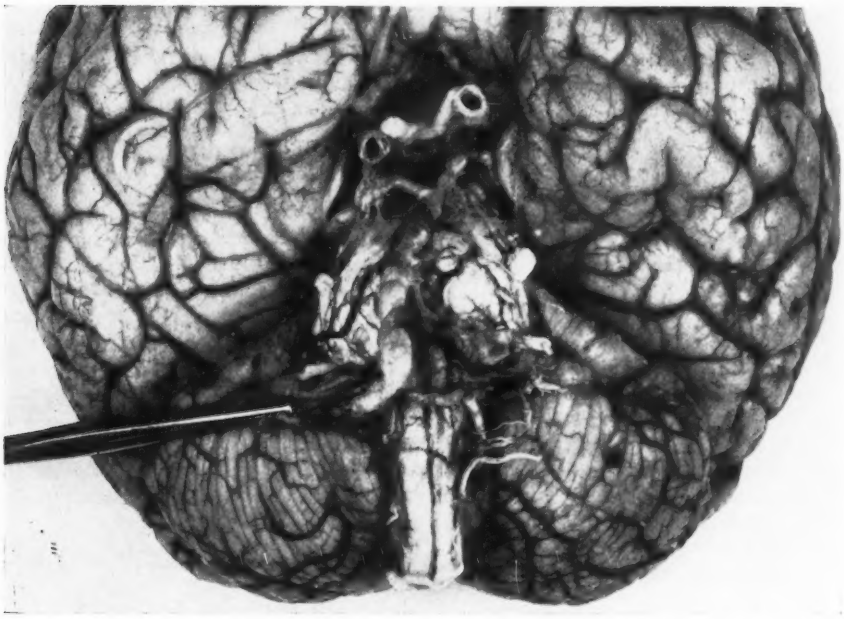

FIG. 3. The left vertebral artery is retracted to demonstrate the depression on the left of the transverse groove. It gives off the left posterior inferior cerebellar artery which runs downwards behind the roots of cranial nerve XII. Cranial nerve IX cannot be clearly distinguished from X.

The right cranial nerves IX, X, XI and XII and the left cranial nerves XI and XII were unaltered but demyelination was seen in several bundles of radicular fibres of the left cranial nerves IX and X (Fig. 4). One of these bundles was almost completely demyelinated; the others were partly demyelinated. Portions of the roots of the left and right cranial nerves IX and X were teased and stained by Sudan: neutral fat was not observed in them.

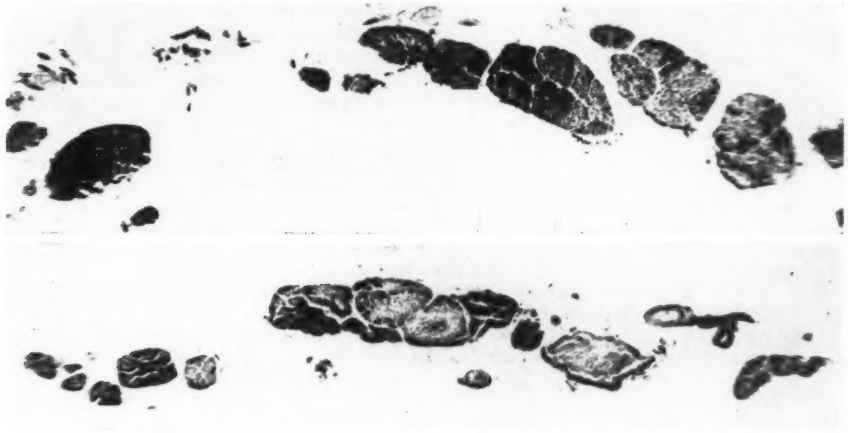

FIG. 4. (*Above*) Radicular fibres of the right cranial nerves IX and X. Their myelin sheaths are intact. (*Below*) Radicular fibres of the left cranial nerves IX and X. Some myelin sheaths are partly and others severely degenerated (Weigert-Pal method).

DISCUSSION

The nonunion of vertebral arteries was regarded as an extremely rare anomaly. McMinn[7] published 1 case, discovered accidentally at dissection, and quoted only 2 other similar observations, one of Berry and Anderson[2] and the other of Batujeff.[1] Frequent use of vertebral angiography has shown, however, that this absence of union of the vertebral arteries is not a rare anomaly. Among 221 patients subjected to vertebral angiography, Radner[9] saw 7 cases—that is to say, nonunion of the vertebral arteries in 3.1 per cent.

Our observation is interesting chiefly because of the etiology of the neuralgia which was related to the pressure of the atheromatous elongated left vertebral artery on the brain stem rather than because of the anatomical anomaly. The paroxysms of pain had the clinical character of "essential" neuralgia in spite of their organic origin. The objective sensory changes in the glossopharyngeal area were not investigated in the present case. If the frequency of the neuralgia among old people is taken into account (30 per cent beyond the age of 60 years according to Schachter[10]) one can imagine that such a compression of radicular fibres of the nerve by a lengthened atheromatous artery is not exceptional. The clinical problem of the dolicho-arteries put forward by Leriche[5] should be considered at the cephalic level. It remains to be explained, however, why the pain occurred so recently, while the malposition of the artery was apparently present for a long time.

SUMMARY

A report on a patient aged 77 years with advanced atheroma who suffered from "essential" glossopharyngeal neuralgia is presented. Postmortem examination disclosed compression of the radicular fibres of the nerve by an elongated, atheromatous vertebral artery. The compressed nerve roots showed partial demyelination. This observation suggests that, in some cases, essential glossopharyngeal neuralgia may be caused by compression of the nerve by an atheromatous artery.

The help of Dr. W. G. P. Mair in correcting the English translation of this paper is gratefully acknowledged.

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IMPROVED SYRINGE FOR ANGIOGRAPHY

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In the technique of cerebral angiography a smooth, quick injection of the contrast material is desirable. If the syringe binds during the injection, as occasionally happens with the standard all-glass type, the continuity of the injection is interrupted. When an increased force is applied to overcome the resistance, there is frequently a sudden surge in pressure which may be sufficient to force apart the syringe and the needle or intervening tubing.

We have deve'oped a special syringe for angiography which does not bind and

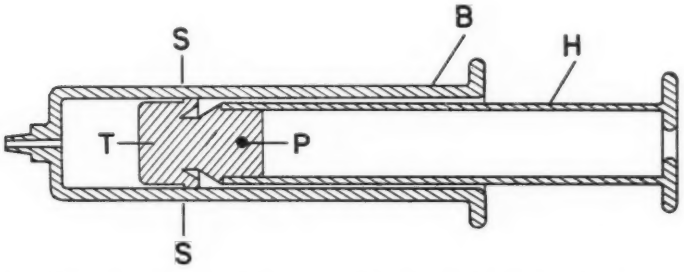

Fig. 1. Special syringe for angiography—section drawing. Barrel, B, is smooth-bore glass (interchangeable) with metal Luer tip. Plunger consists of Teflon end, T, and tubular stainless steel handle, H, joined by a pin, P.

which has certain other advantages.* The syringe consists of a plunger with a Teflon† end and a smooth-bore, glass barrel (Fig. 1). The Teflon is formed in such a way that there is an air-tight ring seal where it makes contact with the glass (S-S, Fig. 1). The resulting friction is moderate and approximately uniform so that the syringe has a smooth action and does not stick. The plunger holds its position during ordinary handling. This prevents inadvertent aspiration of air or loss of fluid after the syringe has been filled.

Fig. 2 shows two of these syringes. The 20 cc. syringe has the advantage of a shorter stroke for the same volume of fluid.

These syringes withstand ordinary use, including steam sterilization. Because of the large coefficient of thermal expansion of Teflon, it is necessary that the plunger and barrel be separated for autoclaving and reassembled for use after cooling.

This type of syringe has been used for more than 100 percutaneous carotid and

* This syringe is a modification of one previously described[1] for analytical work. A patent application has been filed by C. V. Robinson and F. X. Massé. The syringe is obtainable from the MacGregor Instrument Company, Needham, Mass.

† Tetrafluoroethylene polymer (DuPont).

vertebral angiograms during the past 9 months. Since blood does not adhere to the plunger, one syringe may be used for the two to four injections ordinarily necessary for a single study. The use of these syringes has improved the quality of our angiograms as well as the ease of angiography. There have been no complications associated with these angiograms.

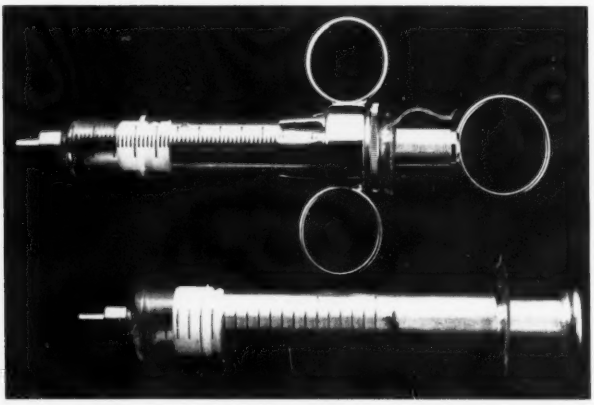

FIG. 2. Twenty cc. syringe and 10 cc. syringe with finger rings.

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STUDIES IN STEREOENCEPHALOTOMY V.

A UNIVERSAL STEREOENCEPHALOTOME (MODEL V) FOR USE IN MAN AND EXPERIMENTAL ANIMALS*

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In the development of stereotaxic operations it became apparent that it is desirable to have an apparatus that permits one to reapply the instrument repeatedly in exactly the same position, e.g. in order to study preoperatively by depth electroencephalography the functional state of a region to be eliminated, or the effect of its transitory elimination by injection of local anesthetics, or in order to perform the operation in several stages. The stereoencephalotome model V to be described is devised for such purposes. It also permits stereotaxic operations in animals by means of a small accessory base.

The instrument is fixed to the skull by 4 hollow stainless steel (Type 316, 18-8 MO) screws (external diameter 6 mm., internal diameter 3 mm., height 8 mm.) which have a flange so that they may be countersunk into the bone. They may remain in the skull for weeks or months. These screws are threaded not only on their outer but also on their inner surfaces so that a threaded stud carrying a small steel ball may be screwed into them. The apparatus (Figs. 1 and 2) rests on 4 stainless steel balls by means of 4 vertical posts (v_{1-4}). These posts consist of a tube in which a graduated bar is movable so that the length of the post may be varied and a certain position of the apparatus (corresponding to certain lengths of the posts) can be easily reproduced. On the lower end of each vertical post there is a spring socket(s) which engages the steel ball and is locked in position when the threaded collar (t) is screwed down. By the same method the upper end of each vertical post is connected to a ball on the lower surface of the basal ring (b). The fixation of the basal ring in a certain position is furthermore insured by extensible graduated oblique posts (o_1–o_3). These are fixed to the vertical posts on their lower end by a small hinge, and their upper end to steel balls protruding obliquely from the lower surface of the basal ring (b) by a similar ball and socket mechanism as above described (visible opposite the label "o_3").

The frame consisting of the vertical posts v_{1-4} and the oblique posts o_{1-3} permit one to quickly align the basal ring (b) in a certain position (usually parallel to the horizontal plane of the head) and to reapply the stereoencephalotome to the skull at operation in exactly the same position as at the time of x-ray examination. This basal ring consists of an outer and an inner part. In the latter a rectangular frame (r) slides forward and backward. By rotating the inner ring, the longer side of the rectangular frame (r) can be brought in a position parallel to the sagittal sinus. The electrode holder can slide on the rectangular frame (r) to the left and right in a lateral direction along transverse dovetails (d). It can also be rotated in the frontal and sagittal planes. Furthermore, the electrode holder can be placed in the transverse dovetails in such a way that the electrode lies outside of instead of within the rectangular frame (Fig. 2). This is important for punctures through the occipital bone, as for instance, in mesencephalotomy or through the frontal bone in pallidotomy. In the former case, the instrument is so positioned upon the skull that the oblique post o_3 lies over the frontal bone,

* Aided by Grant No. B-470 of the National Institute of Neurological Diseases and Blindness of the National Institutes of Health, United States Public Health Service.

while in the latter case it lies over the occipital bone. There is a graduation on the basal ring (g_1) showing the rotation of the inner ring together with the rectangular frame (r) in the horizontal plane, another graduation (g_2) on the longer side of the frame (r) indicating the

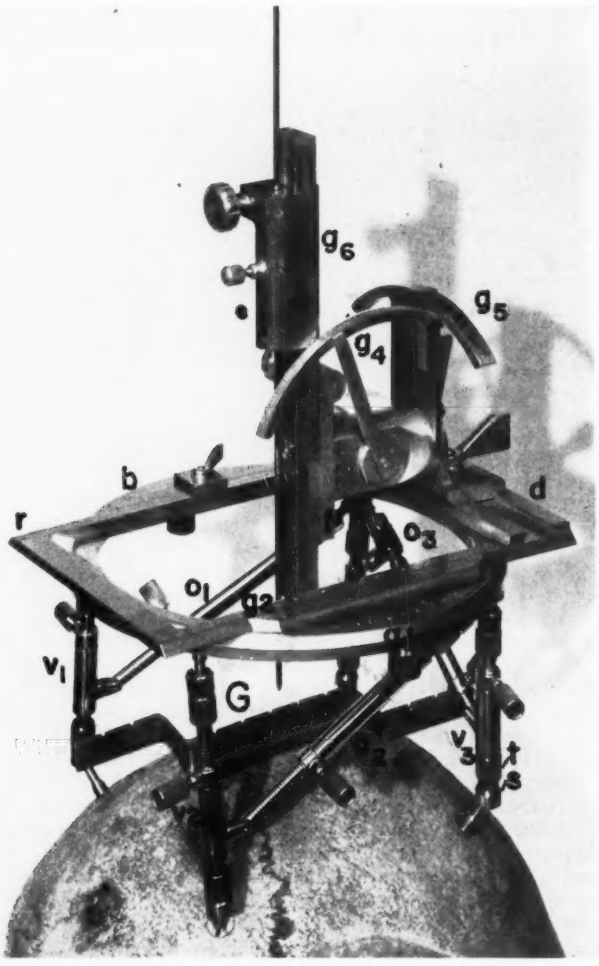

FIG. 1. Stereoencephalotome. b = basal ring, d = transverse dovetails, e = movable part of electrode holder, f = fixed plate of electrode holder, g_1–g_6 = graduations (g_5 on d is not visible in the figure and therefore not marked). G = gauge, o_1–o_3 = oblique posts, r = rectangular frame, s = spring socket, t = threaded collar, v_1–v_3 = vertical posts (v_4 seen on Fig. 2).

position of the electrode holder in an anteroposterior direction, and a third (g_3) on the shorter side of the frame (r) so that the distance of the electrode from the mid-sagittal plane can also be noted. Further graduations indicate the rotation of the electrode holder in the sagittal (g_4) and in the frontal plane (g_5).

The electrode holder consists of 3 parts: a fixed plate (f) against which a graduated plate (g_6) can be moved by hand up and down for coarse adjustment. The electrode holder proper (e) is moved in the same direction against the graduated plate (g_6) by rack and pinion for fine adjustment. The weight of the apparatus is 1 lb.

An accessory frame (AF) not used at operation allows (1) alignment of the basal ring parallel to the horizontal plane and (2) proper positioning of the skull during the x-ray exposure so that the mid-sagittal plane (for lateral roentgenograms), or the interaural plane (for anteroposterior roentgenograms) is parallel to and at a constant distance from the x-ray film. This frame (Fig. 3), which is 28.5 cm. long, 23.5 cm. wide, and 10 cm. high, carries on its under surface graduated ear plugs (p) and orbital bars (or). Rectangular plastic plates form its sides; they have vertical lead marks (l_1–l_4) that are interrupted at 1 cm. intervals and correspond to the mid-sagittal and interaural planes respectively. Along these lead marks the plastic plates have extensions on their upper edges. The corners of the frame AF carry vertical posts V_{5-8}. A spider frame (sf) supporting a circular plastic plate (c) can be attached to

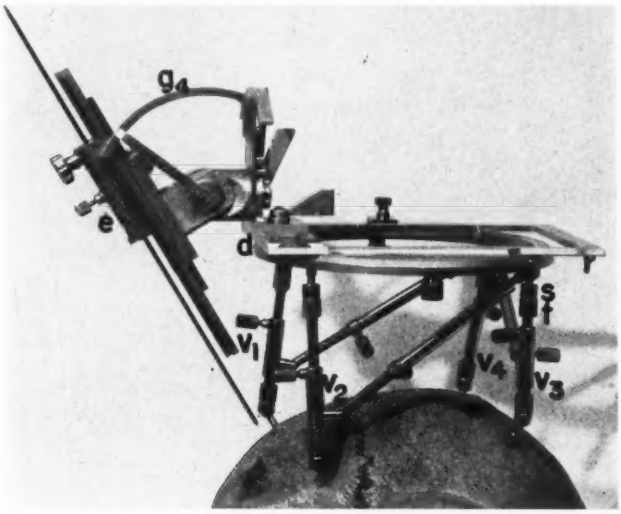

FIG. 2. Anotl er view of apparatus. d = transverse dovetails, e = movable part of electrode holder, g_4 = graduation, r = rectangular frame, s = spring socket, t = threaded collar, v_1–v_4 = vertical posts.

V_5–V_8; on proper placement of the frame (AF), the circular plate lies parallel to the horizontal plane of the skull. It can be moved up and downward in a direction perpendicular to this latter plane. The accessory frame (AF) together with the spider frame (sf) and circular plate (c) weigh 2 11/16 lb. (1 kg., 220 gm.).

In order to align the basal ring (b) parallel to the horizontal plane of the skull, one has to lower the circular plate (c) until it touches the upper surface of the outer part of the basal ring (the inner part with rectangular frame having been removed); then this ring has to be pressed against the circular plate by means of 2 C clamps (cc) so that it is in complete contact with it (Fig. 3). In this position of the ring (b) the screws on the vertical and oblique posts (v_{1-4} and o_{1-3}) are tightened. The lengths of all these posts are noted in order to insure proper realignment at operation.

The accessory frame (AF) is fixed to the stereoencephalotome by means of the longitudinal rods L_1, L_2 that are attached to V_{5-8} and V_{6-7} respectively and that carry the transverse rods T_1, T_2 with the semicircular clamps (sc) fitting into a groove above each threaded

collar (t) of v_1–v_4. The fixation of T_1, T_2 to L_1, L_2 and of the latter to V_{5-8} is obtained by universal clamps (uc) that permit an oblique position of the longitudinal and transverse rods which becomes necessary if the skull screws upon which the stereoencephalotome rests are not located in a plane parallel to the horizontal plane of the skull.

For the x-ray exposures, the plastic circular plate (c) and its spider frame (sf) as well as the ear plugs (p) and orbital bars (or) are removed. The inner part of the basal ring (b) with the rectangular frame (r) is replaced on the apparatus with the movable part of the electrode holder (e) perpendicular to the plane of the basal ring (g_4 and g_5 set at zero position). For

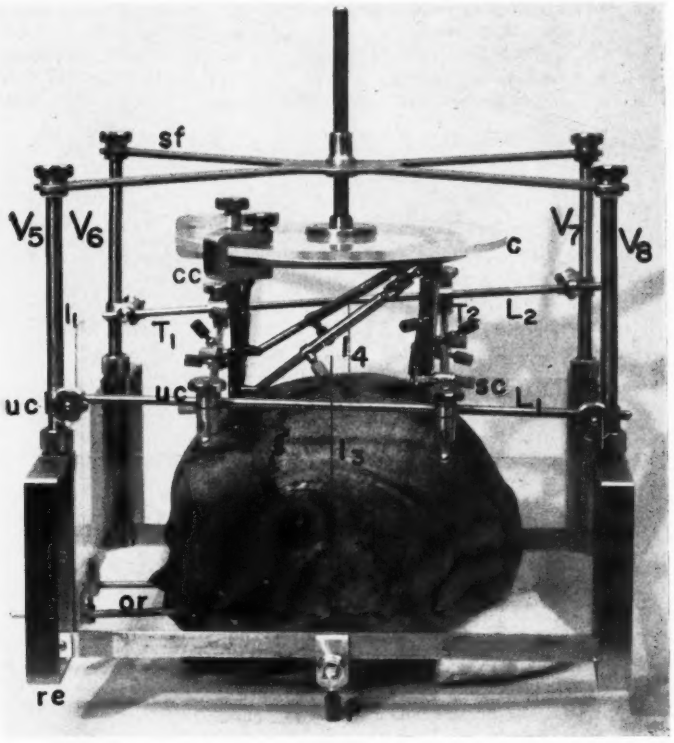

FIG. 3. Auxiliary frame together with stereoencephalotome. c = circular plastic plate, cc = C clamp, l_1–l_4 (l_2 not visible) = lead marks, L_1–L_2 = longitudinal rods, or = orbital bar, p = ear plug, re = rectangular stand-off strip, sc = semicircular clamp, sf = spider frame, T_1–T_2 = transverse rods, uc = universal clamps, V_5–V_8 = vertical posts.

anteroposterior exposures the plastic wall opposite the occipital bone must abut against the surface of the Potter-Buckey diaphragm. For lateral x-ray exposures rectangularly bent stand-off strips (re) attached to the accessory frame (AF) serve this purpose.

The model here described can also be used in animals by placing it upon the base shown in Fig. 4. This base is similar to the one previously devised by Spiegel and Miller[1] for the Horsley-Clarke apparatus. Besides posts for the ear plug holders (p) it contains 4 corner posts (P_1–P_4) that carry steel balls upon which the stereo-

encephalotome rests. The 2 anterior posts (P_1, P_2) carry also an upper transverse bar on which the orbital bars (or) slide and a lower chin bar (ch) that slides in slits and presses the animal's chin upwards, so that the lower rim of the orbit is pressed against the orbital bars. The head is fixed by a Czermak head holder that is attached to the animal board to which the base is also clamped.

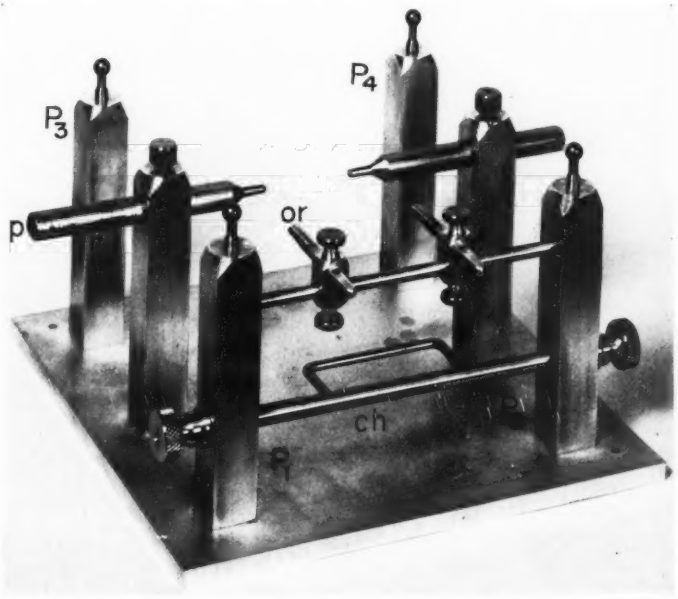

FIG. 4. Base for animal experiments. ch = chin bar, or = orbital bar, p = ear plug holder, P_1–P_4 = posts.

SUMMARY

A stereoencephalotome has been devised that can be applied repeatedly in exactly the same position. It weighs only 1 lb. In conjunction with an accessory base it can also be used for animal experiments.

REFERENCE

1. SPIEGEL, E. A., and MILLER, H. R. Stand for aseptic operations with Horsley-Clarke's stereotaxic instrument. *J. Lab. clin. Med.*, 1941, *26:* 1657–1658.

NOTICES

AMERICAN NEUROLOGICAL ASSOCIATION

The 81st annual meeting of the American Neurological Association will be held at the Claridge Hotel, Atlantic City, New Jersey, June 18–20, 1956, under the Presidency of Johannes M. Nielsen, M.D. of Los Angeles, California.

All communications regarding the meeting should be addressed to Charles Rupp, M.D., Secretary of the Association, 133 South 36th Street, Philadelphia 4, Pennsylvania.

NATIONAL INSTITUTES OF HEALTH

The Public Health Service has announced a new procedure to expedite the processing of research grant applications for those requests that do not exceed $2000 plus indirect costs and that do not ask support for more than one year. Such applications will be accepted and processed on receipt and are not therefore subject to the usual deadlines for submission prior to review.

Council recommendations can be expected on these applications within 1–4 months from the time of submission. These procedures do not apply for requests for supplements to existing grants.

Address all applications as well as requests for forms or additional information to the Division of Research Grants, National Institutes of Health, Bethesda 14, Maryland.

NEUROSURGICAL SOCIETY OF AMERICA

The 9th annual meeting of the Neurosurgical Society of America was held at Key Biscayne, Florida, January 18–21, 1956. The following officers were elected: President, I. Joshua Speigel; Vice-Presidents, Lester A. Mount and Robert Watson; Secretary, Frank P. Smith; Treasurer, Bertram Selverstone.

The next meeting will be held in Palm Springs, California, January 16–19, 1957. The meeting is intended for the members and invited guests.

SOUTHERN NEUROSURGICAL SOCIETY

At the 8th annual meeting of the Southern Neurosurgical Society held in Jacksonville, Florida, March 23 and 24, 1956 the following officers were elected: President, Dr. W. Gayle Crutchfield, Charlottesville, Virginia; Vice-President, Dr. William F. Meacham, Nashville, Tennessee; Secretary-Treasurer, Dr. C. D. Hawkes, Memphis, Tennessee.

JOURNAL OF NEUROSURGERY

The *Journal of Neurosurgery* is devoted to the publication of work relating primarily to neurosurgery, including studies in clinical neurophysiology, organic neurology, ophthalmology, radiology and pathology. Short articles on unusual cases and on technique, special instruments or equipment that might be useful to others in the field are also acceptable.

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